University of Southampton

Faculty of Environmental and Life Sciences (FELS)

Health Sciences

Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors Associated with A Prolonged QT Interval in Term Neonates (37 Weeks Gestation or Greater) When It Is Assessed on an Electrocardiogram at 48 – 72 Hours of Age

Volume 1 of 1

By

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Thesis for the degree of Doctor of Clinical Practice

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Abstract

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Selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressants which when utilised in pregnancy are known to increase the risk of prematurity and neonatal abnormalities including persistent pulmonary hypertension of the newborn, congenital defects and withdrawal symptoms. SSRIs are also known to prolong the QT interval in the electrocardiogram of adults, which can lead to sudden death, but limited data are available for neonates.

This prospective case-controlled study therefore sought to examine whether there was an association between antenatal exposure to SSRIs and a prolonged QT interval on the electrocardiogram of term (37 weeks gestation or greater) neonates at 48- 72 hours of age. A group of neonates who were exposed to SSRIs in utero received an electrocardiogram at 48-72 hours old (case group). They were compared with healthy neonates whose mothers did not take SSRIs in pregnancy, but who were still in hospital at 48-72 hours (control group). Of the 43 case neonates and 45 control neonates who had an electrocardiogram (ECG), all had a normal QT interval when screened at 48-72 hours old. Most of the women who used antenatal SSRIs were being treated for depression and/or anxiety with sertraline being the most commonly used SSRI.

No association was found between antenatal exposure to SSRIs and a prolonged QT interval in term neonates when assessed at 48-72 hours old, however the study was underpowered, and the result should be interpreted with caution.

Based on these findings, there is no justification to change practice and implement an ECG screening programme as part of postnatal care for SSRI exposed neonates. Further research may be considered, but based on this study's feasibility would not be warranted within the current fiscal climate of the NHS

Table of Contents

Word Count: - 46,878

Table of Tables

Table of Tables

Table of Figures

Table of Figures

Table of Figures

Research Thesis: Declaration of Authorship

Print name:	Marie Lindsay-Sutherland

Title of thesis:	Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors Associated with a Prolonged QT Interval in Term Neonates (37 Weeks Gestation or Greater) When it is Assessed on an Electrocardiogram at 48 – 72 Hours of Age

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

Where I have consulted the published work of others, this is always clearly attributed;

Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

I have acknowledged all main sources of help;

Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

None of this work has been published before submission

Signature:	Marie Lindsay-Sutherland	Date:	12/ 05/ 2019

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Definitions and Abbreviations

ADHD	Attention deficit hyperactivity disorder
ANNP	Advanced neonatal nurse practitioner
AOR	Adjusted odds ratio
ASD	Atrial septal defect
AV node	Atrial ventricular node
CBT	Cognitive behavioural therapy
CI	Confidence interval
CRP	C- reactive protein
DGH	District General Hospital
EBP	Evidence based practice
ECG	Electrocardiogram
ECHO	Echocardiogram
EPR	Electronic patient record
FDA	Food and drug administration agency
GCP	Good clinical practice
GDPR	General data protection regulation
GI	Gastro-intestinal
GP	General practitioner
hERG	Human ether-a-go-go related gene
LQTS	Long QT syndrome
MCA	Maternity care assistant
Msecs	Milliseconds
NAS	Neonatal abstinence syndrome

NHS	National health service
NICE	National institute for health and care excellence
OR	Odds ratio
PPHN	Persistent pulmonary hypertension of the newborn
QTc	QT interval
RCT	Randomised controlled trial
RR	Relative risk
RVOTO	Right ventricular outlet tract obstruction
SA Node	Sinoatrial node
SIDS	Sudden infant death syndrome
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitors
TdP	Torsades de pointes
UK	United Kingdom
US	United States
5-HT	Serotonin

Glossary of Terms

Term	Meaning
Advanced neonatal nurse practitioner	Specially trained neonatal nurse following a medical model and leading care for sick, term and preterm infants along with the neonatal medics
ALERT	Antenatally generated plan for postnatal plan of care
Amniotic fluid	Protective fluid around fetus
Analgesics	Pain relief
Ano-rectal atresia	Malformed rectum with a blind ending/ missing exit point
Ano-rectal stenosis	Narrow rectal opening
Antenatal	During Pregnancy
Antidepressants	Medication used for treatment for depression
Anti-emetics	Medication to stop nausea and vomiting
Anti-hypotensives	Medication to correct low blood pressure
Anti-reflux	Medication to stop heartburn
Anti-tricyclic antidepressants	Medication for mental health disorders. Created in 1950's.
Apgar scores	Subjective assessment of colour/ tone/ activity/ heart rate/ respiration rate at birth
Atrial septal defect	Abnormality in the wall of the top portion of the heart
Attention deficit hyperactivity disorder	Mental health disorder where have difficulty controlling behaviour.
C reactive protein	Blood marker for infection
Caesarean section	Being born via an abdominal route
Cardiac	Relating to the heart
Cardiology	Relating to the heart
Category D drug in pregnancy	Medications which if taken in pregnancy are known to cause abnormalities in the baby

Term	Meaning
Central nervous system	Brain and spinal cord
Clinical fellow	Junior doctor
Cognitive behavioural therapy	Psychosocial intervention- coping strategy
Confidence level	Statistical estimate that the observed data contains the right answer
Containment	Placing of hands to mimic the support/ comfort of the uterus
Cortisol	Steroid hormone produced in response to stress
Craniosynostosis	Early fusing of skull bones so brain can't develop properly
Cystic kidneys	Swelling in kidney affecting function
Depolarisation	When the charge within the cell moves from negative to neutral
Diabetes	Disorder of blood sugar balance
District General Hospital	Major health care facility for region
ECG axis	Direction of the overall electrical activity of the heart
Echocardiogram	Pictorial representation of the heart using ultrasound
Electrocardiogram	Pictorial representation of heart beat
Epilepsy	Neurological disorder which presents with seizures
Extrapyramidal symptoms	Neurological effects of withdrawal from certain drugs. Includes jitteriness, restlessness, spasms and rigidity
Fetus	Unborn baby
First trimester	0-12 week of pregnancy. Full development of fetus
Gastroschisis	Intestine extending outside of the body through a hole next to the belly button. Present at birth
General practitioner	Lead community health professional.
Genital	Relating to sex organs
Gestation	Period of development of baby from conception to birth
Hypospadias	Urethral opening is not at head of penis as usual

Term	Meaning
Hypothyroidism	Disorder where inadequate levels of the hormone thyroxine are produced
Instrumental delivery	Being born via forceps or ventouse method
Midwife	Professional who specialises in childbirth
Morbidity	Prevalence of a diseased state
Myocytes	Cells found in muscle tissue.
Neonatal abstinence syndrome	Withdrawal symptoms from drug exposure
Neonatal consultant/ Neonatologist	Senior Doctor who manages the care of babies
Neonatal period	Birth to 28 days old
Neonate	Newborn baby less than 4 weeks old
Neurology	Relating to the nervous system
Neurotransmitter	Chemical messenger- transmits signal across a synapse
Normal vaginal delivery	Being born via the vagina- normal method of birth
Omphalocele	Abdominal wall defect where intestines/ liver/ other organs remain outside of abdomen. Present at birth
P value	Statistical gauge of probability that the test idea is maintained or rejected
Paediatric	Relating to children aged from birth to 18 years old
Paediatrician	Doctor who manages the care of children
Persistent pulmonary hypertension of the newborn	Failure to convert from the fetal to normal circulation after birth. High mortality rate
Placenta	Organ that connects a fetus to the uterine wall. Provides gaseous exchange and waste elimination
Positional talipes	Turning in of feet from position in the uterus- muscular only- not fixed
Postnatal	Up to 8 weeks after birth.
Postnatal depression	Depression after the birth of a baby

Term	Meaning
Pregnancy	Time when a baby is developing inside the woman
Premature	Baby born before 37 weeks gestation
Pulmonary	Relating to lungs
QT interval	The time between the depolarisation and repolarisation of the ventricles of the heart
Renal	Relating to the kidney
Repolarisation	When the charge within the cell moves from neutral back to negative after depolarisation
Respiratory distress of the newborn	Breathing problems around the time of birth/ in the immediate newborn period
Second trimester	13-27 weeks of pregnancy. Key time for lung development
Selective serotonin re-uptake inhibitors	Medication for mental health disorders. Created in 1980's. Class of antidepressants
Sepsis	Infection
Serotonin	Neurotransmitter
Serotonin-norepinephrine reuptake inhibitor	Medication for mental health disorders. Class of antidepressants created in 1994.
Synapse	Structure that allows nerve cells to pass an electrical / chemical signal to another nerve cell
Syncope	Fainting
Talipes equinovarus	Turning in / out of feet. Fixed position. "club foot"
Tertiary hospital	Referral hospital providing full range of specialist care
Third trimester	28-42 weeks of pregnancy. Key time for growth and weight gain
Tongue tie	Extra piece of skin anchoring tongue into position
Torsades de Pointes	Arrhythmia that can occur in those with a long QT interval
Ultrasound	Pictorial way of viewing inside of the body
Vasculature	Blood vessels/ circulation system

Introduction and Background

1 Introduction and Background

1. 1 Rationale for Study

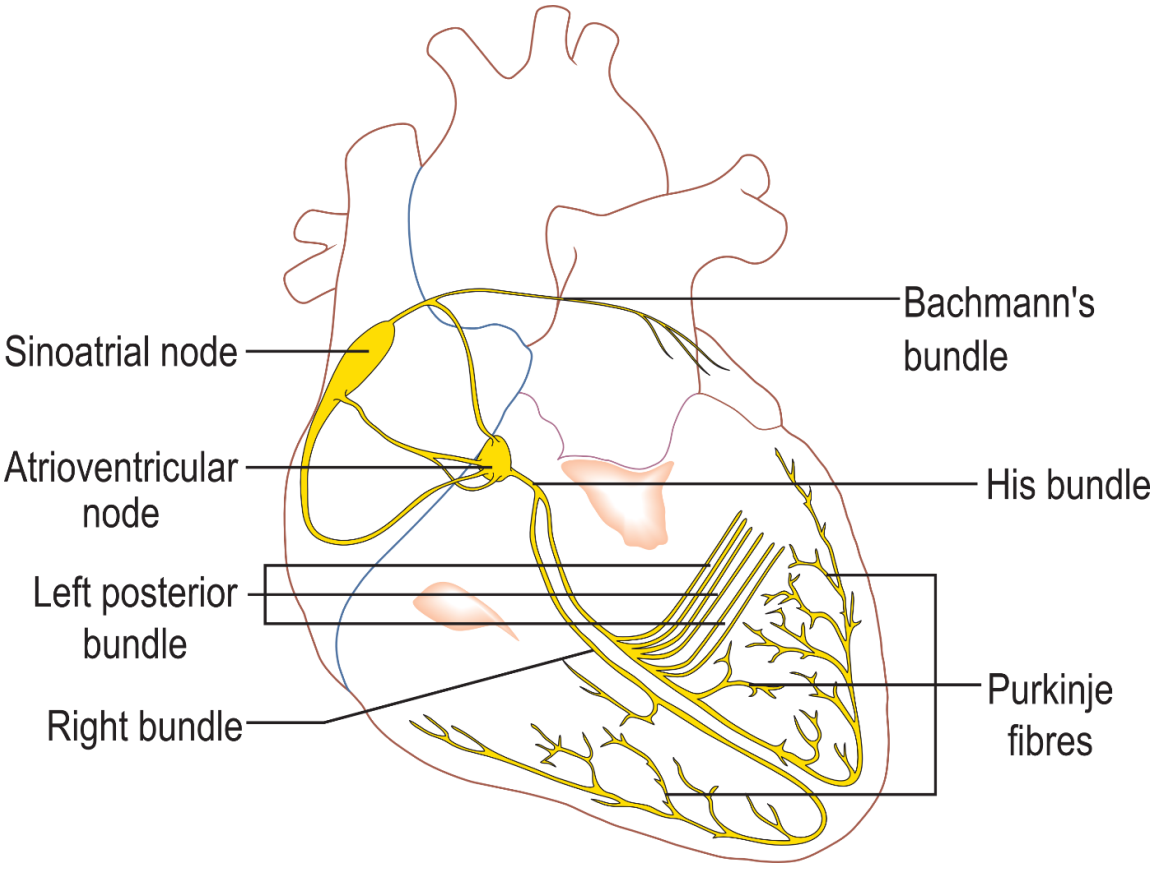
As the lead advanced neonatal nurse practitioner (ANNP) in a District General Hospital (DGH), I provide and direct care for premature (less than 37 weeks gestation), term (37 weeks gestation and above) and sick neonates. Part of my role is the generation and documentation of an evidenced based postnatal plan (ALERT) (appendix A) for women who have taken any medication in pregnancy. As a result of this work, I became acutely aware of the growing usage of a group of antidepressants called selective serotonin reuptake inhibitors (SSRIs) in the birthing population. In 2010, I generated 60 postnatal plans for antenatal use of SSRIs, and this had increased to 120 ALERTs three years later. This was in the context of a NICE mental health pathway recommendation for moderate and severe depression, which endorsed the use of SSRIs in pregnancy being adopted by the DGH (*[Local area] National Health Service (NHS), 2016).

Concurrent to clinical practice, I started my doctoral journey in order to achieve personal and professional enhancement with regard to current evidenced based neonatal practice. This thesis is the culmination of a doctoral programme that has provided theoretical and practical application of clinical leadership for quality improvement, clinical governance, decision making, advanced neonatal clinical practice and research theory. The academic programme has confirmed the importance of a specialty- specific and contemporaneous evidence base in the provision of high-quality clinical care for neonates and their families. The academic skill set gained as part of this programme and the opportunities afforded by my clinical role, has supported the development of this study to address the apparent limited data that examine the effect of antenatal SSRIs on the QT interval of the

electrocardiogram (ECG) in a term neonate, and to ensure the ALERTs are contemporaneously evidence based.

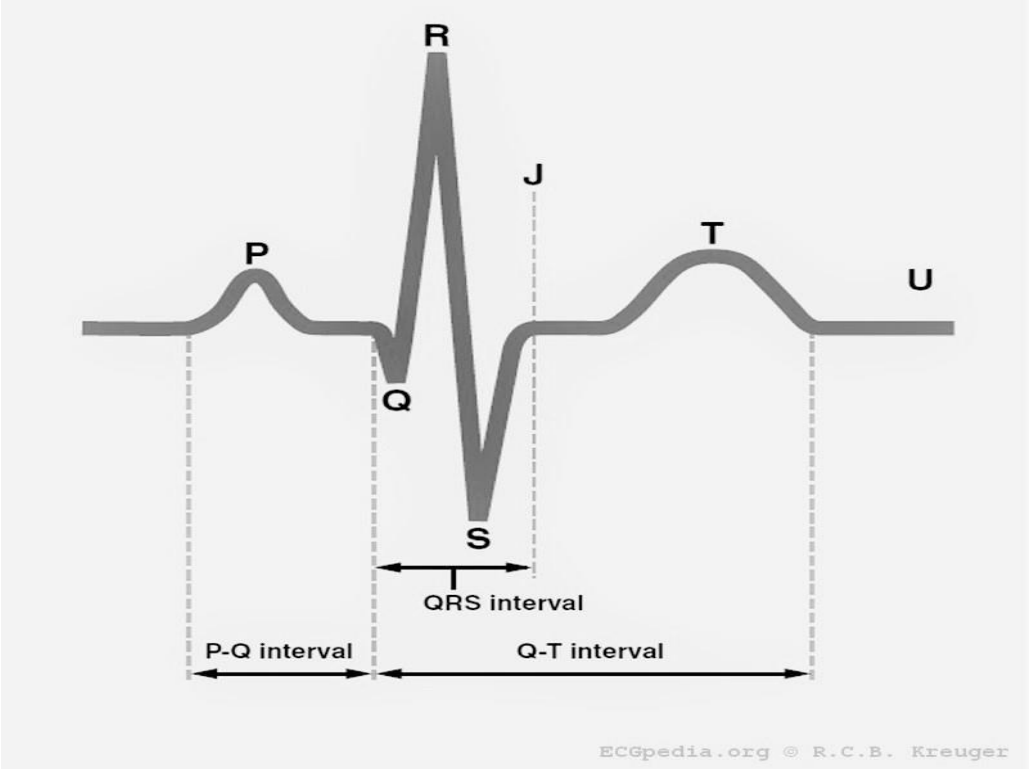
The QT interval is part of the cardiac electrical system. Specialised cardiac muscle cells, myocytes, are responsible for the generation of electrical impulses which control heart rate. Electrical impulses arise in the sinoatrial (SA) node in the right atrium of the heart (figure 1. 1).

Figure 1. 1 The Electrical Conduction System of the Heart (Madhero88, 2010)



The impulse then spreads across the right atrium and the left one, causing atrial depolarisation (p-wave on ECG- figure 1. 2).

Figure 1. 2 ECG Wave (ECG Pedia. Org, 2013a)



Depolarisation is the neutralisation of the negative charge generated. After this the impulse travels to the atrioventricular (AV) node (figure 1. 1). Here the impulse is slowed to allow the blood to be ejected from the atria to the ventricles. Electrical impulses then travel to the base of the ventricles from the bundle of His, thus causing ventricular depolarisation, neutralising the generated negative electrical charge there (QRS complex on an ECG- figure 1. 2) (Becker, 2006). The repolarisation or rest period in the ventricles is represented by the T wave on an ECG (figure 1. 2) (Becker, 2006).

The timing of the repolarisation in the myocytes is regulated by human Ether-a-go-go related gene (hERG) channels. Repolarisation involves the movement of potassium through the hERG channels (Rajamani et al, 2006). SSRIs are known to block this movement of potassium (Becker, 2006) and therefore prolong the QT interval, that is the electrical depolarisation and repolarisation, of the left and right ventricles of the heart to greater than 440 milliseconds, which is the widely accepted parameter, as reported by the European Society of Cardiology (Schwartz et al, 1998; Schwartz et al, 2002). However, in an in-vitro study, SSRIs were found to block the hERG channels in this way only when the channels are open, thus limiting potential effects (Thomas et al, 2002).

SSRIs are also thought to reduce the number of hERG channel proteins in the surface membrane, and therefore prolong the QT interval by that means (Becker, 2006). These actions can cause irregularities in the ions and irregular heartbeats, which can lead to an arrhythmia called Torsades de Pointes (Witchel, 2007) (appendix D), and thereafter syncope and potential sudden death in adults. It is hypothesised that fetal exposure to antenatal SSRIs may lead to similar significant effects in the neonate.

The next section details the structure of the thesis, so the reader is orientated to the various sections of this research journey before progressing to discuss the background to the study.

1. 2 Structure of Thesis

Having identified the research topic as a result of my clinical role, section 1. 3 presents the background to the study. It demonstrates the burden that mental health

disorders place on the woman and neonate, and treatment options currently available. A critical appraisal of the existing research establishes that there is an increased risk of a prolonged QT interval in SSRI exposed adults, and of prematurity, persistent pulmonary hypertension of the newborn (PPHN), congenital abnormalities and clinical signs of withdrawal in the neonate from antenatal exposure to SSRIs. The apparent limited data that describe the effect of SSRIs taken in pregnancy on the neonatal QT interval of the ECG are also highlighted, and inform the literature search that is detailed in chapter two to verify this gap in knowledge. This literature search was limited to 2005 and later due to the proliferation of research that occurred after a Food and Drug Administration Agency (FDA, 2006) judgement regarding a specific SSRI. Three papers were retained from this search, two case studies (Degiacomo et al, 2016; Dubnov et al, 2005) and a case-controlled study (Dubnov-Raz et al, 2008), all of which reported a prolonged QT interval in antenatally SSRI exposed neonates.

The methodology and methods utilised in the study, which were developed to test the null hypothesis in regard to the confirmed gap in knowledge, are detailed in chapter three. This includes the philosophical underpinning of the study, as well as sample selection, inclusion /exclusion criteria, and the process of data collection including ECG. Normal clinical practice is presented for both the case and control groups as it underpins the research method. Further, this chapter explains the mode of analysis for the data, the management of and the follow up for neonates with ECG abnormalities, and the storage of the data during and after study completion. Finally, ethical considerations are explored and how they were managed is detailed.

Chapter four provides an extensive analysis of the resulting study data. The primary outcome data regarding the QT interval value itself, the range of QT interval values achieved across the groups, and age in hours at which the ECG was taken, are all explored. ECG abnormalities that occurred are described and the review of the electronic patient records at six months of age stated. This chapter also analyses the

secondary outcomes, regarding maternal mental health disorders, the SSRIs used by the women in the case group and any unknown associations between the antenatally SSRI exposed and unexposed neonate. Demographic data for all women and neonates are also presented.

Chapter five discusses the results of this study and how it compares to other published data. How the study is positioned within national and worldwide initiatives is also highlighted. The strengths and weaknesses of the study methodology and method are then discussed. Finally, chapter six reflects on the implications of the study and its results for clinical practice, personal practice and education. Recommendations for future studies are stated and plans for dissemination of the study's findings and the research process are detailed, before concluding comments are offered.

All reference to the study hospital and local area are anonymised along with any publications that the locality have produced. This anonymisation is to provide additional protection and maintain the privacy for those from whom data were collected (Information Commissioner's Office, 2012). All figures, except figure 3.6, are free from copyright or are compliant with Creative Commons BY-SA 3.0 Attribution – ShareAlike Licensing standards, which permit reproduction/ amendment for correctly referenced figures (https://creativecommons.org/licenses/by-sa/3.0/). Figure 3.6 was generated by myself. Abbreviations and definitions are tabulised on pages xxiii- xxiv. A glossary of terms is found on pages xxv- xxix.

The research process starts with clarification of the incidence of mental health disorders in pregnancy and this is detailed in the next section. Following that, the implications for the mother and neonate from not treating mental health disorders are described, and current available treatment options are discussed.

1. 3 Background

1. 3. 1 Incidence of Mental Health Disorders in Pregnancy

Depressive symptoms affect 10- 20% of pregnant women worldwide (Courtney, 2009; Freeman, 2007; Hanley et al, 2014; Homberg et al, 2009; Jimenez-Solem et al, 2012; Louik et al, 2007; Medicines & Healthcare Products Regulatory Agency UK, 2014; *[Local area] NHS UK, 2016; WHO, 2016). Depressive symptoms are described as low mood, low esteem, tearfulness, agitation, increased or decreased appetite, fatigue, feeling worthless, lacking motivation and thoughts of suicide (NHS UK, 2019a). In the UK, data based on 116,457 women who had at least one live birth and attended their General Practitioner (GP) in the nine months prior to pregnancy, found that 9.3% had been diagnosed with depression (mood disorder that causes a persistent feeling of sadness and loss of interest (NHS UK, 2019b)), 4.1% suffered with anxiety disorders (intense, excessive and persistent worrying and fear about everyday events (NHS UK, 2019b)) and 0.12% had other serious mental health problems (Schizophrenia, Psychosis, severe depression and Bipolar disorder (NHS UK, 2019b)) (Ban et al, 2012). There was some overlap between the maternal perinatal mental illnesses, but 7.2 %, 2.1% and 0.04% respectively had depression, anxiety disorders and other serious mental health problems alone (Ban et al, 2012). The reported prevalence of depression and anxiety disorders occurring in pregnancy was less, being 4.2% and 1.7% respectively (Ban et al, 2012). Pregnancy reporting of other serious mental health problems was the same as pre-pregnancy (0.04%). Within the antenatal care pathway, pregnant women are assessed for depressive symptoms. Any concerns at these times, trigger GP review and assessment for management. Whilst not all these women would have required pharmacological treatment during pregnancy, the burden on families and mental health services is evident.

1. 3. 2 Implications of Not Treating Mental Health Disorders in Pregnancy

Untreated maternal anxiety and any form of stress in pregnancy leads to an increased release of cortisol, which in turn increases the cortisol levels in the fetus (Glover, 2011). This surge is thought to affect brain programming in the fetus and increase the risk of emotional disorders (Hanley et al, 2014); attention deficit hyperactivity disorder (ADHD) (Pearlstein, 2008; Talge et al, 2007); sleep disturbances (Monk et al, 2011) and language delay in the child (El Marroun et al, 2012; Pearlstein, 2008).

Untreated maternal stress can lead to a reduction of blood flow to the placenta which increases the risk of a low birth weight neonate (El Marroun et al, 2012; Hanley et al, 2014; Jarde et al, 2016; Koren et al, 2012; Olivier et al, 2011); prematurity (El Marroun et al, 2012; Fenger-Gron et al, 2011; Hanley et al, 2014; Jarde et al, 2016; Koren et al, 2012; Olivier et al, 2011); low Apgar scores at birth (Fenger-Gron et al, 2011); admission to the neonatal unit (Olivier et al, 2011); smaller head size (El Marroun et al, 2012); and pregnancy loss (Koren et al, 2012). Goedhart et al (2010) in their large prospective cohort study found that antenatal women with elevated levels of depressive symptoms were more likely to smoke more than those with lower levels of depressive symptoms (14.4% versus 7.4%). Smoking in pregnancy itself can cause placental deterioration and insufficiency, which also can lead to premature birth, a lower birth weight and reduced resilience during the birthing process, and this impact should be acknowledged in studies looking at maternal mental health concerns.

Luskin et al (2007) stated that those women with untreated depression were more likely to have poor weight gain, poor sleep patterns and were less likely to engage with antenatal services. This lack of wellbeing in pregnancy and reduced fetal surveillance may lead to compromise for both the woman and the fetus. Freeman (2007) also highlighted how untreated depression affects bonding between the

mother and baby, potentially due to the increased risk of postnatal or severe depression from non-treatment (Jarde et al, 2016). Finally, and the most serious impact, there is also a potential increased risk of suicide (Luskin et al, 2007; *[Local area] NHS UK, 2016), with the associated impact on the family. Not treating mental health disorders can therefore lead to long term consequences for both the woman and the neonate (*[Local area] NHS UK, 2016) so all pregnant women need to receive the most appropriate treatment.

1. 3. 3 Treatment Options for Mental Health Disorders in Pregnancy

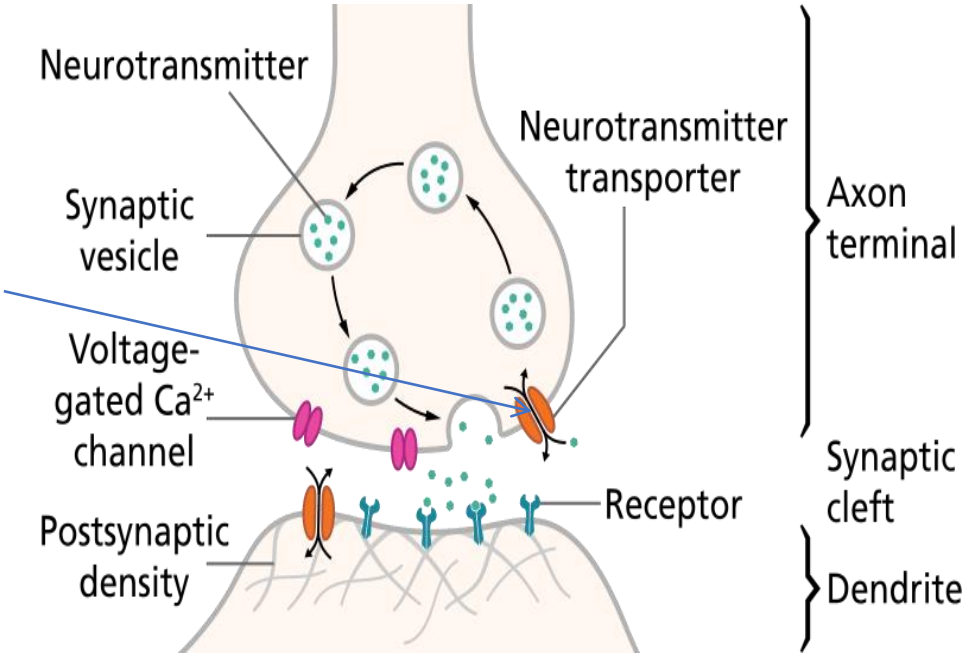
Treatment options for women with mental health disorders include cognitive-behavioural therapy (CBT) and medication such as SSRIs. CBT is useful for mild symptoms of mental health disorders through provision of short courses of supportive therapy, however, availability may be limited (NHS UK, 2015; *[Local area] NHS UK, 2016). Medications therefore form the mainstay of treatment and accordingly there has been an increasing global trend in the use of SSRIs to treat mental health disorders (Andrade et al, 2016; Jimenez-Solem et al, 2013) (appendix B). SSRIs are a class of antidepressants developed in the 1980's when animal studies observed that inhibition of serotonin (5-HT) reuptake by neuroreceptors promoted improved mood, against a background of low circulating 5-HT levels (Booij et al, 2015). In the brain, messages between nerve cells travel via a synapse. The presynaptic cells release neurotransmitters such as serotonin into the gap. These neurotransmitters are then received by neuroreceptors in the postsynaptic cell.

There is a loss of 10% of these neurotransmitters before they are processed by the presynaptic cells again. Inhibition of reabsorption leads to increased levels of serotonin in the synapses, the terminal point of the nerve (Lattimore, 2005) (figure 1. 3). Due to the ability of SSRIs to raise serotonin levels by these means, they are used

to treat major depression, but are also utilised in the management of generalised anxiety disorder, obsessive compulsive disorder, phobias, post-traumatic stress disorder and panic disorders (NHS Choices, 2015).

Figure 1. 3 Diagram Demonstrating the Process by Which Neurotransmitters Such as Serotonin are Reabsorbed and How SSRIs Can Block This Process (Splettstoesser, 2015)(Amended)

Inhibition here by SSRI would block re-uptake of serotonin, increasing levels in the synapse



Although their effectiveness for mild to moderate depression has been questioned (Fournier et al, 2010; Kirsch et al, 2008), SSRIs continue to be the main pharmacological choice for mental health disorders, including in pregnancy, and data shows their increasing usage. Data from the United States (US) (Andrade et al 2008), Europe (Bakker et al, 2007) & the United Kingdom (UK) have all demonstrated an increase in SSRI usage since the mid 1990's. Indeed, Bakker et al (2007) utilised pharmacy databases in the Netherlands to ascertain that SSRI dispensing in

pregnancy had increased from 12.2 per 1000 in 1995 (95% CI 7.0- 19.8) to 28.5 per 1000 in 2003/4 (95% CI 23.0- 34.9). Whilst not specifically SSRIs in pregnancy, antidepressant prescriptions have increased from 2.9% of all prescriptions in 1998, to 3.98% in 2012 in England (Health and Social Care Information Centre, 2014). Indeed, for the English population, there has been an associated increase in the number of Primary Care Trusts that issue more than 200 prescriptions for antidepressants per 1000 people from 29 in 2010/11 to 63 in 2012/13 (Health and Social Care Information Centre, 2014).

1. 3. 4 Potential Effects of SSRIs on the Fetus/ Neonate (Excluding the Cardiac Electrical System)

Before 2005, the risk of major abnormalities in the neonate resulting from antenatal exposure to SSRIs, was believed to fall within the expected rate of 1- 3% for the general population (Einarson et al, 2008). SSRIs are known to cross the placental barrier and be present in the amniotic fluid in concentrations similar to that in the mother's blood and potential adverse effects have become more evident (Roca et al, 2011). Different 5-HT neuroreceptors and proteins develop at various points in gestational age, and therefore disruption at key developmental times in embryologic development and maturation may impact on the fetal central nervous system (Booij et al, 2015), pulmonary vasculature (Belik, 2008), the heart system (Dubnov- Raz et al, 2010) as well as long term emotional effects on the child (Booij et al, 2015).

A FDA judgement questioning the safety of the use of the SSRI paroxetine in pregnancy, stimulated the generation of research in 2005 (FDA, 2006). The potential fetal and neonatal effects of exposure to SSRIs in pregnancy has been the focus of much research, but often with conflicting findings due to lack of randomised controlled trials and lack of adjustment for confounders such as mental health disorders,

smoking and social background, which may increase the frequency of any negative associations noted (sections 1. 3. 4 .1; 1. 3. 4. 2; 1. 3. 4. 3; 1. 3. 4. 4). Studies have found an association between SSRI use in pregnancy and PPHN (Norby et al, 2016; Reis et al, 2010), prematurity (Huang et al, 2014; Ross et al, 2013), neonatal abstinence syndrome (Levinson-Castiel et al, 2006) and congenital abnormalities such as cardiac defects (Berard et al, 2015).

One study also found neonates who were antenatally exposed to SSRIs were more likely to be admitted to the neonatal unit than the normal population (13.7% v 8.2%; Adjusted Odds Ratio (AOR) = 1.5, 95% CI 1.4-1.5) (Norby et al, 2016). The risk of neonatal unit admission was further compounded with late pregnancy SSRI exposure v early (16.5% v 10.8%; AOR=1.6, 95% CI 1.5-1.8) (Norby et al, 2016). The causes of the admission to the neonatal unit included respiratory distress of the newborn, hypoglycaemia and PPHN. In addition, recent research has suggested neurodevelopmental effects, motor developmental delay and autism spectrum disorders are more likely in the exposed population (Man et al, 2015; Olivier et al, 2015; Videmann et al, 2017), although other studies have found no increased risk of these three outcomes (Brown et al, 2017; Sujan et al, 2017).

The following sections provide greater detail on the studies which focus on the effects of this group of antidepressants on the fetus and neonate. Different methodologies which evaluate SSRIs are considered in turn, namely health database studies, case-control studies and finally meta-analyses studies. This methodological division reflects the hierarchy of evidence and demonstrates the validity of statistically analysed results within the research topic. The tables in the following sections also provide a clear means by which to assess studies with differing results for the same pathology. Further, as stratification for individual SSRIs has occurred within large studies, the effects of fluoxetine, paroxetine, sertraline and citalopram on the cardiac

structure is also presented. Literature and systematic reviews are however detailed in appendix C as no extra statistical analysis is provided. Finally, the cardiac electrical system is reviewed separately due to its link to the research topic.

1. 3. 4. 1 Observational Database Studies Examining the Effects of SSRIs on the Fetus/ Neonate (Excluding the Cardiac Electrical System)

Many observational studies have retrospectively and prospectively reviewed health or pharmaceutical databases which utilise large cohorts, here ranging from 3,764 to 2.1 million participants, and found a significant association between SSRI exposure in pregnancy and certain pathologies. Two studies (Kallen et al, 2008; Reis et al, 2010) found a 2.4- 3.6 times increased risk of PPHN in the neonate antenatally exposed to any SSRI versus the unexposed neonate (table 1.1). PPHN is a rare condition occurring in only 2: 1000 neonates but has a high mortality rate of 4- 33% (Shah et al, 2015), so the impact of this increased rate from SSRI exposure is considerable.

The observational studies that examined the rate of craniosynostosis, the premature fusion of the sagittal suture of the skull, found that twice the number of neonates were affected in the antenatally SSRI exposed group versus those not (Berard et al, 2015; Jimenez-Solem et al, 2012) (table 1.1). There was also found to be an increased rate of talipes equinovarus (Colvin et al, 2011; Wemakor et al, 2015), hypospadias (Reis et al, 2010) and renal defects (Wemakor et al, 2015) in those neonates exposed to any SSRI antenatally versus those not exposed (table 1.1). Additionally, there was a 1.8 – 2.5 increase in gastrointestinal defects in the SSRI exposed population (Jimenez-Solem et al, 2012; Wemakor et al, 2015) but confidence intervals were widened with two of the defects (table 1.1). Exposed infants were also more likely to be born prematurely (Reis et al, 2010) (table 1.1).

Table 1. 1 Observational Studies Which Utilised Health Databases and Found a Significant Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of Database/ Registry Studies	Setting/ Cohort	Results
PPHN	Kallen et al, 2008;	Sweden. 1997-2005. 831, 234 newborns in total. 7587 mothers used SSRIs antenatally. 11 had PPHN.	RR= 3.6; 95% CI, 1.2 - 8.3 (late exposure) RR= 2.4; 95% CI, 1.2 – 4.3 (early exposure)
	Reis et al, 2010	Total of 1019514 infants (1995-2007). Sweden. 15,017 infants exposed to SSRI	OR=3.44; 95% CI 1.49- 6.79
cardiac abnormalities	Berard et al, 2015	1998-2010. Quebec.18493 pregnancies. 2329 SSRI AN. 61 had cardiac abnormalities v 344 unexposed	OR=1.34; 95% CI 1.02- 1.76 (ASD- sertraline)
craniosynostosis	Berard et al, 2015	1998-2010. Quebec.18493 pregnancies. 2329 SSRI AN. 21 of exposed had craniosynostosis v 63 of unexposed	RR=2.03; 95% CI 1.09- 3.75
	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183 had SSRI exposure in early	OR=1.94; 95% CI 1.00- 3.76

Pathology	Authors of Database/ Registry Studies	Setting/ Cohort	Results
		pregnancy. 9 had craniosynostosis	
talipes equinovarus	Colvin et al, 2011	Western Australia. 2002-2005. 123,405 pregnancies with 3764 exposed infants.	OR=1.52; 95% CI 0.75–3.08
	Wemakor et al, 2015	EUROCAT Countries.1995-2009.2,177,977 total births. 328 pregnancies with SRRI use. 30 exposed had defect v 1992 unexposed.	OR=2.41; 95% CI 1.10- 5.29
hypospadias	Reis et al, 2010	Total of 1019514 infants (1995-2007). Sweden 15,017 infants exposed to SSRI. 38 had hypospadias	OR=2.45; 95% CI 1.12- 4.64 (paroxetine)
gastroschisis	Wemakor et al, 2015	EUROCAT Countries.1995-2009.2,177,977 total births. 328 pregnancies with SRRI use. 7 exposed had defect v 413 in unexposed.	OR=2.4; 95% CI 1.10- 5.29
omphalocele	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183	OR 1.80; 95% CI 1.04- 3.12

Pathology	Authors of Database/ Registry Studies	Setting/ Cohort	Results
		had SSRI exposure in early pregnancy. 13 had gastro-intestinal defects v 1545 unexposed.	
ano-rectal atresia and stenosis	Wemakor et al, 2015	EUROCAT Countries.1995-2009.2,177,977 total births. 328 pregnancies with SRRI use. 6 had defects in exposed v 392 in non-exposed	OR=2.46; 95% CI 1.06- 5.68
cystic kidneys	Wemakor et al, 2015	EUROCAT Countries.1995-2009.2,177,977 total births. 328 pregnancies with SRRI use. 12 had defects in exposed v 618 in non-exposed	OR= 3.01; 95% CI 1.61- 5.61
Prematurity	Reis et al, 2010	Total of 1019514 infants (1995-2007). Sweden. 15,017 infants exposed to SSRI 356 were premature	OR=1.46; 95% CI 1.31- 1.63

However, some observational studies utilising health database records did not replicate the findings detailed above and found no association between SSRI

exposure in pregnancy and craniosynostosis, omphalocele, genital defects, renal defects or talipes equinovarus (table 1. 2).

Table 1. 2 Observational Studies Which Utilised Health Databases and Found No Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of Database/ Studies	Setting/ Cohort	Results
craniosynostosis	Kallen et al, 2007	Sweden. 1995-2004. 6555 neonates with AN SSRI exposure. 6 exposed had defect v 612 unexposed	RR= 1.53; 95% CI 0.56- 3.33
omphalocele	Kallen et al, 2007	Sweden. 1995-2004. 6555 neonates with AN SSRI exposure. 3 exposed had defect v 316 unexposed	RR=1.16; 95% CI 0.24-3.40
talipes equinovarus	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183 had SSRI exposure in early pregnancy. 53 had defect v 11,785 in unexposed.	OR= 0.93; 95% CI 0.71 to 1.23
renal defects	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183 had SSRI exposure in early pregnancy. 11 had defect v 2333 in unexposed	OR= 0. 84, 95% CI 0.45 to 1.57
genital defects	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183 had SSRI exposure in early	OR= 1.32; 95% CI 0.71 to 2.46

Pathology	Authors of Database/ Studies	Setting/ Cohort	Results
		pregnancy. 19 had defect v 2504 in unexposed	
	Kallen et al, 2007	Sweden. 1995-2004. 6555 neonates with AN SSRI exposure. 26 exposed had defect v 3162 unexposed	OR=1.18; 95% CI 0.8- 1.75

Due to research design, these observational studies utilising database records are unable to adjust for confounders such as mental health disorders, smoking and social background which may affected outcomes. Often the databases are designed for other purposes and the data extracted are not specific to the research topic. Furthermore, databases are at risk of bias from poor input of data. Some of the studies utilising database records also used data pertaining to prescriptions filled as proxy to actual ingestion. Studies have shown that 20-50% of pregnant women don't take SSRIs as prescribed, demonstrating the potential for bias, and weakening the validity regarding reported incidence rate (Jimenez-Solem et al, 2012; Koren et al, 2012; Ray et al, 2014). Despite the varying degree of certainly /uncertainty for specific adverse effects noted above (table 1.1 and 1.2), the evidence does suggest that SRRIs do have an impact and therefore it is important that the best evidence is available for those considering or who are pregnant and being medicated with SSRIs.

1. 3. 4. 2 Cohort and Case- Control Studies Examining the Effects of SSRIs on the Fetus/ Neonate (Excluding the Cardiac Electrical System)

Cohort and case- control studies which examined the effects of SSRIs on various aspects of a fetus or neonate, had smaller sample size than the database studies, but still included moderate size cohorts of 120- 17,952 participants. For some conditions their findings are consistent with some of the database studies, as is the case for PPHN (Chambers et al, 2006), talipes equinovarus (Louik et al, 2007; Yazdy et al, 2014), prematurity (Davis et al, 2007), gastrointestinal defects (Louik et al, 2007; Reefhuis et al, 2015), craniosynostosis (Reefhuis et al, 2015) and for cardiac defects (Knudsen et al; 2014; Louik et al, 2007) (table 1.3). A cohort study also found that up to 30% of neonates developed the extrapyramidal symptoms that indicate neonatal abstinence syndrome (NAS), either as a direct effect of antenatal SSRI exposure or as a consequence of withdrawal from the medication (Levinson-Castiel et al, 2006) (table 1.3). However, no cohort/ case-control studies specifically stated an association in regard to renal defects or hypospadias as reported in the database studies in table 1.1, indeed two studies (Davis et al, 2007; Louik et al, 2007) stated there was no association between SSRI exposure in pregnancy and hypospadias (table 1.4).

Table 1. 3 Cohort/ Case -Control Studies Which Found a Significant Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of Cohort/ Case- Control Studies	Setting/ Cohort	Results
PPHN	Chambers et al, 2006	USA.1998-2003. 377 had PPHN: matched controls= 836. Blinded nurses contacted parents at 6 months of age and SSRI use was included in telephone interview.	OR of 6.1; 95% CI 2.2 -16.8
NAS	Levinson-Castiel et al, 2006	Set in tertiary unit in Israel. 2002- 2004. 23,254 births -> 60 exposed to paroxetine/ fluoxetine/ sertraline: 60 unexposed. Finnegan score/ HR/RR monitored.	30% incidence exposed v unexposed (p=<0.001)
prematurity	Davis et al, 2007	USA. Research trial in 5 hospitals. 1047 prescribed SSRIs. 166 exposed born early v 5268 unexposed	RR=1.45; 95% CI 1.25-1.68
cardiac abnormalities	Knudsen et al; 2014	Denmark.1995-2008. 72,280 total pregnancies. 845 women used SSRIs in pregnancy. 11 exposed had defect v 546 unexposed.	OR=4.03; 95% CI 1.75- 9.26

Pathology	Authors of Cohort/ Case- Control Studies	Setting/ Cohort	Results
talipes equinovarus	Louik et al, 2007	USA. 1993-2004. 9849 infants with defects and SSRI exposure. 20 with defect in exposed v 413 not exposed	OR= 2.2; 95% CI 1.4- 3.6 OR=5.8; 95% CI 2.6- 12.8 (paroxetine)
	Yazdy et al, 2014	USA. 2006-2011. 622 infants with talipes v 2002 non deformed controls.	OR= 1.8; 95%CI 1.1- 2.8
omphalocele	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 3 with defect v 127 not exposed	OR=5.7; 95% CI 1.6- 20.7 (sertraline)
	Reefhuis et al, 2015	USA. 17,952 infants with birth defects v 9857 with no defects.1997- 2009.	OR= 3.5; 95% CI 1.3- 8.0 (paroxetine)
gastroschisis	Reefhuis et al, 2015	USA. 17,952 infants with birth defects v 9857 with no defects.1997- 2009.	OR= 2.5; 95% CI 1.2- 4.8 (paroxetine)
craniosynostosis	Reefhuis et al, 2015	USA. 17,952 infants with birth defects v 9857 with no defects.1997- 2009.	OR=1.9; 95% CI 1.1- 3.0 (fluoxetine)

Pathology	Authors of Cohort/ Case- Control Studies	Setting/ Cohort	Results
anal atresia	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 7 exposed with defect v 215 unexposed	OR= 4.4; 95% CI 1.2-16.4 (sertraline)

Other case- control / cohort studies did not reflect the associations found in large observational population-based studies and the studies detailed in table 1.3 (table 1.4). Louik et al (2007) did not find an association between antenatal SSRI exposure and craniosynostosis in the neonate, and no association was found with cardiac defects (Davis et al, 2007; Knudsen et al, 2014). There was no increased risk of prematurity found in the Venkatesh et al (2016) study, although both database studies and other cohort/ case-control studies had found such an association.

Table 1. 4 Cohort/ Case -Control Studies Which Found No Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of Cohort/ Case- control Studies	Setting	Results
prematurity	Venkatesh et al, 2016	USA. 2010-2013. 7,267 total cohort. 160 received AN antidepressants.	OR=1.01; 95% CI 0.99- 1.02
cardiac abnormalities	Davis et al, 2007	USA. Research trial in 5 hospitals. 1047 prescribed SSRIs. 10 exposed had defect v 672 not exposed	RR=0.93; 95% CI 0.50- 1.73
	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 100 exposed had defect v 3724 unexposed	OR= 1.2; 95% CI 0.9- 1.6
craniosynostosis	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 2 exposed had defect v 115 unexposed	OR= 0.8; 95% CI 0.2-3.5
omphalocele	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 3 exposed had defect v 127 unexposed	OR=1.4; 95% CI 0.4- 4.5 (all SSRIs)
hypospadias	Davis et al, 2007	USA. Research trial in 5 hospitals. 1047 prescribed SSRIs. 16 exposed had	RR=0.82; 95% CI 0.50- 1.34

Pathology	Authors of Cohort/ Case- control Studies	Setting	Results
		defect v 1152 not exposed	
	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 14 exposed had defect v 497 unexposed	OR=1.2; 95% CI 0.6- 2.2

Despite the continuing varying degree of certainty and the methodological weakness of case- control/ cohort studies meaning only an association or lack of it can be stated, the evidence still suggests that SRRIs do have an impact especially in regard to PPHN, some structural abnormalities and NAS.

Even with large cohorts, there are still wide confidence intervals where the adverse effect is rare. Within all these studies, the confidence intervals range from 1.2 - 20.7 but the widest ranges relate to PPHN (background rate of 2 per 1000 neonates (Shah et al, 2015)) and omphalocele (rate of 1 per 5386 neonates (The Centers for Disease Control and Prevention, 2015)). To improve validity of these studies, several meta-analyses were undertaken in the subject area and these are detailed in the next section.

1. 3. 4. 3 Meta-analyses Examining the Effects of SSRIs on the Fetus/ Neonate (Excluding the Cardiac Electrical System)

Whilst meta-analyses achieved narrower confidence intervals with regards to an association for SSRI exposure in pregnancy with prematurity (Huang et al, 2014; Ross et al, 2013) and cardiac abnormalities (Bar-Oz et al, 2007), some of the meta-analyses were limited as they were based on only a few good quality case - control studies. The method by which the meta-analyses were undertaken was rigorous where stated. There was varying heterogeneity noted within the meta-analyses, with Huang et al (2014) reporting high levels and Man et al (2015) having low. There was also disparity noted with the controls in the included studies, with them being depressed on non-SSRIs, not depressed, or having untreated depression, which may have impacted on the results. This is also the first methodology that has looked at neurological effects such as motor developmental delay in the neonate with SSRI exposure in pregnancy (Man et al, 2015). Evidence is inconclusive regarding this neonatal effect and further literature reviews on this research area are listed in appendix C.

Table 1.5 Meta-analyses Which Found a Significant Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of meta-analyses	Setting	Results
prematurity	Huang et al, 2014	Start- 2012. USA. 28 studies included.	RR= 1.69; 95% CI 1.52-1.68
	Ross et al, 2013	Canada. Start- 2010. 23 studies included.	OR=1.55; 95% CI 1.38- 1.74

Pathology	Authors of meta-analyses	Setting	Results
cardiac abnormalities	Bar-Oz et al, 2007	Canada. Meta-analysis of case control/ cohort studies.1985-2006. All studies included 1st trimester exposure to paroxetine v control of pregnant unexposed. Abnormalities only relating to live births.	OR 1.72; 95% CI 1.22-2.42
neurological effects	Man et al, 2015	Start- 2014. 15 studies were included.	OR= 2.13; 95% CI 1.66-2.73

Finally, one further meta-analysis of four cohort studies found no association between first trimester SSRI exposure and cardiac abnormalities (table 1. 6).

Table 1.6 Meta-analyses Which Found a No Significant Association Between SSRI Exposure in Pregnancy and Certain Pathologies

Pathology	Authors of meta-analyses	Setting	Results
cardiac abnormalities	Wang et al. 2015	China. Start -2014. 4 cohort studies.	OR= 1.06; 95% CI 0.94-1.18

1. 3. 4. 4 Individual SSRIs and Their Effect on the Fetal / Neonatal Cardiac System (Excluding the Cardiac Electrical System)

Some studies found a significant association with one medication within the SSRI drug class but not all the drug class. This was particularly relevant to cardiac abnormalities. Initially, paroxetine was implicated with regards to neonatal cardiac defects, but as usage of all the drug class has increased, it has become evident that all have the potential to cause cardiac abnormalities in the neonate. Indeed, Jimenez-Solem et al (2012) stated that citalopram, fluoxetine and sertraline all increased the risk of cardiac defects. Berard et al (2015) found an increase in atrial septal defects with sertraline and Reefhuis et al (2015) found a 1.8 x increase with paroxetine. Both Reefhuis et al (2015) and Louik et al (2007) found increased rates of right ventricular outflow tract obstruction defects in the heart with paroxetine, and similarly, two studies had this finding with fluoxetine (Bar-Oz et al, 2007; Reefhuis et al, 2015).

Table 1.7 Studies Which Found a Significant Association Between a Specific SSRI and a Pathology

Pathology	Authors	Setting	SSRI	Result
all cardiac abnormalities	Jimenez-Solem et al, 2012	Denmark. 1997-2009. 848,786 pregnancies. 4183 had SSRI exposure in early pregnancy. 77 exposed neonates had a cardiac abnormality	Citalopram fluoxetine sertraline	OR=1.91; 95% CI 1.31- 2.77 OR=2.05; 95% CI 1.27- 3.31 OR= 2.73; 95% CI 1.75- 4.26

Pathology	Authors	Setting	SSRI	Result
atrial septal defects	Berard et al, 2015	1998-2010. Quebec.18493 pregnancies. 2329 SSRI AN-386 to sertraline. 9 of exposed v 272 of unexposed had ASD.	sertraline	OR=1.34; 95%CI 1.02- 1.76
	Reefhuis et al, 2015	USA. 17,952 infants with birth defects v 9857 with no defects.1997-2009.	paroxetine	OR= 1.8; 95% CI 1.1- 3.0
right ventricular outflow tract obstruction defects	Reefhuis et al, 2015	USA. 17,952 infants with birth defects v 9857 with no defects.1997-2009.	paroxetine fluoxetine	OR= 2.4; 95% CI 1.4- 3.9 OR= 2.0; 95% CI 1.4 – 3.1
	Bar-Oz et al, 2007	Canada. Meta-analysis of case control/ cohort studies.1985-2006. All studies included 1st trimester exposure to paroxetine v control of pregnant unexposed. Abnormalities only relating to live births	fluoxetine	OR=2.0; 95% CI 1.4- 3.0
	Louik et al, 2007	USA.1993-2004. 9849 infants with defects and SSRI exposure. 6	paroxetine	OR=3.3; 95% CI 1.3- 8.8

Pathology	Authors	Setting	SSRI	Result
		exposed had defect v 363 unexposed		

The previous sections have demonstrated the breadth of research detailing the effects of SSRIs across all physiological systems. Despite the varying results across the methodologies from the higher levels of evidence, there are clearly large amounts of data supporting an impact on the neonate from exposure to antenatal SSRIs. However, one area where there is a notable lack of large-scale research, is the effects on the electrical components of the neonatal cardiac system from in utero exposure and this aspect is reviewed in the following section.

1. 3. 5 SSRI Effects on the QT Interval of the Neonatal Cardiac Electrical System -What is Known and What is Unknown

SSRIs have been shown to prolong the QT interval in adults (Funk et al, 2013) but its effect on the neonatal QT interval is still uncertain. The next section details how a prolonged QT interval can lead to sudden death in neonates, including its link to defects of serotonin transmitter morphology. Finally, data are described on the effect of SSRIs on the QT interval in animals, adults and neonates.

1. 3. 5. 1 Sudden Infant Death Syndrome

Schwartz et al (1998) found in their large prospective study of nearly 35,000 neonates, that 12 of the 24 deaths labelled as sudden infant death syndrome (SIDS), had a prolonged QT interval when an ECG was performed on day three or four of life. SIDS are sudden deaths in infancy for which no cause can be found on autopsy, but

are thought for some of the cases to be multi-factorial (The Lullaby Trust, 2018). 89% of SIDS occur before 6 months of age, and in 2015, 216 infants died in the UK from this disorder (The Lullaby Trust, 2018). Defects of 5-HT neurotransmitters caused by both genetic and environmental factors (Awtry et al, 2003) have been implicated in SIDS (Kinney et al, 2009) with a presumed antenatal origin. As stated earlier, different 5-HT neuroreceptors and proteins develop at various points in gestational age, and therefore disruption at key developmental times in embryologic development and maturation may impact on vital organs including the cardiac system (Dubnov- Raz et al, 2010). Indeed, cardiac ion channelopathies have been implicated as a causative factor (Wang et al, 2007), and long QT syndrome accounts for 12% of SIDS (Loakeimidis et al, 2017). Whilst showing an association between 5-HT and SIDS, none of these studies were in the context of SSRI exposure in pregnancy and dealt with a rare event with resulting small numbers of affected infants.

1. 3. 5. 2 A Prolonged QT Interval from SSRI Exposure

Animal studies, were varying doses of SSRIs have been administered, have reported prolongation of the QT interval. In their small study with 12 isolated rabbit hearts, Frommeyer et al (2016) found exposure to citalopram prolonged the QT interval (2 µM: +47 msecs, 4 µM: +56mecs, $P<0.05$), and Kogut et al (2013) reported five out of 10 beagles receiving larger than therapeutic doses of oral citalopram died suddenly from Torsades de Pointes at 17 -31 weeks old. The outcomes in adult human studies are less conclusive. In a systematic review by Funk et al (2013), therapeutic levels of escitalopram was found to prolong the QT interval, however sertraline and fluoxetine did not produce a clinically significant affect. Conversely, Balwant et al (2016) compared 187 naïve patients using escitalopram versus sertraline, and found no significant effect on the QT interval in either group. Funk et al (2013) however did state that many case reports detail an effect from SSRI use on the QT interval. Often human studies focus on older adults who have comorbidity factors such as cardiac

disease and Parkinson's disease (Wilting et al, 2006), and who often are prescribed several medicines with the potential to prolong the QT interval such as sodium channel blockers, beta-blockers and antibiotics (Carceller-Sindreu et al, 2017; Ninkovic et al, 2016; Sovari et al, 2015) (appendix D). There is also a significant risk of a prolonged QT interval in type 2 Diabetes (15.4- 67%), in females more than males (Ninkovic et al, 2016), with inflammatory bowel disease (49% in females) (Pattanshetty et al, 2016), with electrolyte imbalances (Widimsky, 2008) and also genetic long QT syndrome which occurs in up to 1: 10000 (Sovari et al, 2015). So, transferability of data from such pathologies to the predominantly clinically well, younger pregnant population and their offspring is undetermined.

Where a prolonged QT interval in adults resulted from the ingestion of SSRIs in greater than therapeutic dosages, data were available from a younger population (Boer et al, 2005; Rajamani et al, 2006). A prolonged QT interval has been observed in fluoxetine, citalopram, sertraline and escitalopram overdose (Boer et al, 2005; Hayes et al, 2010; Rajamani et al, 2006). The FDA highlighted citalopram as particularly culpable in prolonging the QT interval in adults and especially women, and guidance on medication dosage for those older than 65 years old and those with hepatic impairment has been issued (Medicines and Healthcare Products Regulatory Agency UK, 2011; Vieweg et al, 2012). Escitalopram was also found to have a dose dependent effect on the QT interval (Medicines and Healthcare Products Regulatory Agency UK, 2011).

It is therefore theorised that fetal exposure in pregnancy to SSRIs, with their long half-life and active metabolites (Ray et al, 2014), and the effect of 5-HT on embryological development, in conjunction with reduced neonatal hepatic drug metabolism (Daud et al, 2016), may lead to exposure to drug levels that can cause significant effects such as a prolonged QT interval. Indeed one paper (Dubnov-Raz et al, 2008) did find an increased risk of a prolonged QT interval in antenatally SSRI exposed neonates.

However one of the included antenatally exposed neonates was premature, and four of the other included neonates had their QT interval assessed prior to 30 hours of age, when the QT interval is undergoing a period of postnatal transition and is more variable (Ulrich et al, 2014) and liable to type 1 error. The Dubnov-Raz et al (2008) paper will be discussed later in greater depth in section 2. 2.1.

1. 3. 6 The ALERT System

From the pregnancy booking process to the delivery of the neonate, the woman has numerous contacts with health professionals. If during those contacts, any known or potential concerns that may impact the fetus/ neonate are highlighted, a document, the ALERT, is generated by the midwife, GP or Obstetrician . These concerns may pertain to fetal abnormalities, fetal growth, maternal medical history including depression or anxiety, maternal medicine use that could impact fetal development or postnatal neonatal course, or indeed any other potential issue that requires a management strategy. During such maternal contact with health services, the ALERT is completed for those women who utilise SSRIs in pregnancy. The ALERT is completed with which SSRI is used, the dosage of SSRI used, when the SSRI was commenced, any change to the SSRI used in the pregnancy, as well as what the woman has already been told about the normal postnatal pathway. Formal assessment by a medical professional of the mental health issues that were reported and documented were presumed to have occurred at the point of commencement of medical management with SSRIs.

The ALERT document is then forwarded to the ANNP ALERT Co-ordinator in the neonatal unit, and then disseminated to myself. My role includes the generation and documentation of the postnatal plan for each woman determined by the SSRI used. These ALERT documents are then copied for both the obstetric and neonatal teams

and forwarded to the midwife for discussion with the woman so that she is fully informed regarding the expected postnatal course. These ALERTS need to be appropriately evidence- based and therefore incorporate the body of work detailed above that demonstrates various pathology from antenatal SSRI exposure on the neonate. This process of generating the evidence- based postnatal plan of care however demonstrated that the evidence base seemingly lacked data on the effects of SSRIs on the neonatal QT interval. The apparently limited data provided the focus for a literature search and was the impetus to set up this study within the context of doctoral study, and shape the research question: -

"*Is antenatal exposure to selective serotonin reuptake inhibitors associated with a prolonged QT interval in term neonates (37 weeks gestation or greater) when it is assessed on an electrocardiogram at 48 – 72 hours of age?"*

As SSRIs have been linked to prematurity (Courtney, 2009; El Marroun et al, 2012; Fenger-Gron et al, 2011; Hanley et al, 2014; Jarde et al, 2016; Koren et al, 2012; Olivier et al, 2011) and the QT interval is more variable in the preterm (Ulrich et al, 2014), the focus for the research question is those neonates who at 37 weeks gestation or greater, are classed as term. In addition, it was anticipated that such a study would demonstrate the pattern of SSRI usage, the range of SSRIs used, maternal mental health problems within the case group and may also reveal other differences between the SSRI exposed and the unexposed populations.

1. 3. 7 Summary

This section has revealed the scale of mental health disorders during pregnancy and discussed the consequences for the neonate from both untreated and treated mental

health disorders. This impact includes prematurity, low birth weight, PPHN, NAS and congenital abnormalities. This section has also highlighted that there seems to be a lack of research on the effects of antenatal exposure to SSRIs on the neonatal QT interval with only one known study suggesting a prolonging effect (Dubnov-Raz et al, 2008). This apparent gap in knowledge could therefore be usefully verified by an extensive literature review.

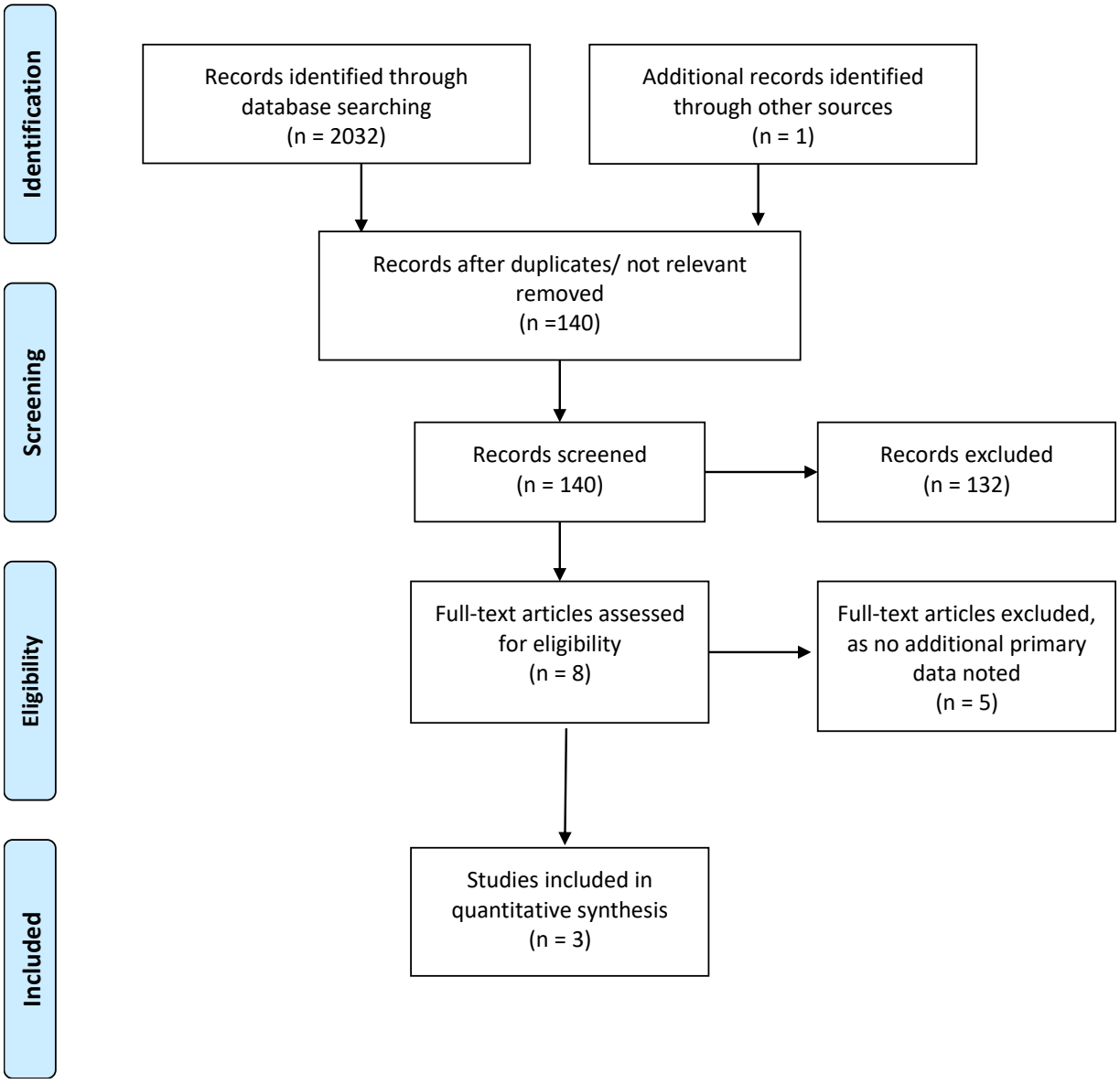
2 Literature Search and Review

The following section details the literature search undertaken to assess the evidence base regarding the effects of antenatal exposure to SSRIs on the neonatal QT interval. The literature review that follows utilises a theoretical, methodological and empirical framework (Bakare, 2013). Firstly, the papers obtained from the literature search are critically analysed to establish what is known about the focus of the review. Further, the methodological approach critiques the methods used in the retained papers in relation to the hierarchy of evidence. Finally, the empirical approach tests the hypothesis of no association with regard to antenatal exposure to SSRIs and the QT interval of the neonate and the alternative hypothesis that there could be. This framework is utilised to confirm the lack of evidence regarding the drug exposure effect on the QT interval of the neonatal that has been suggested in the previous chapter.

2. 1 Literature Search

An extensive literature search was therefore undertaken (appendix E) and a summary of the process is detailed in figure 2. 1 below.

Figure 2. 1 Literature Search Summary (Utilising PRISMA Flow Diagram (Moher et al, 2009)



2. 1. 1 Databases Searched

A systematic search of 27 online databases was undertaken. This electronic search sought to discover full text, English language papers that reported human data and which focused on assessing the gap in knowledge with regard to antenatal exposure to SSRIs on the neonatal QT interval. The literature search timeframe was limited to between January 2005 and April 2018. Although SSRIs were developed in the late 1980's, the generation of research regarding SSRIs escalated significantly after publication of FDA guidance on paroxetine in pregnancy in 2005 (FDA, 2006). This judgement created a natural timeframe for this literature search.

The databases that were searched were: - AMED/ CINAHL/ Medline/ PsycINFO; Clinical Trials.Gov; Cochrane; Delphis; EMBASE/ OVID Medline/ Journals @ OVID/ Your Journals @OVIDfulltext including PsycArticles/ OVID Medline Epub ahead of print, In Process and Other Non- Indexed Citations/ OVID Medline @Daily/ OVID Medline and Versions ®; EU Clinical Trial Register; IBSS; Google; MIDIRS; NICE; Open Grey; Prospero; Scopus; TRIP; Web of Science; WHO Clinical Trials; and Zetoc.

2. 1. 2 Search Terms Used for Literature Search

To meet all aspects of the focus for the literature review, the following search terms were utilised where an advanced search permitted their input:

(QT OR ECG OR EKG OR cardi* OR electrocardio) AND (neonate OR neonat* OR newborn OR baby OR child) AND (SSRI OR selective serotonin reuptake inhibitors OR SRI OR citalopram OR escitalopram OR dapoxetine OR fluoxetine OR paroxetine

OR sertraline OR indalpine OR fluvoxamine) AND (pregnan* OR antenatal*). Where advanced searching was not available, the key aspects were reviewed individually.

2. 1. 3 Inclusion and Exclusion Criteria for the Literature Search

The papers deemed to be relevant were obtained and assessed against the inclusion and exclusion criteria for the literature search as detailed in table 2. 1.

Table 2. 1 Inclusion and Exclusion Criteria for the Literature Search

Inclusion Criteria
The article was published between January 2005 and April 2018
All design methodologies
Related to human studies
Published in English language
Full text available
Papers focusing on antenatal exposure to SSRIs and its effects on the cardiac electrical system of the fetus/ neonate.
Exclusion Criteria
Unable to establish whether the inclusion criteria met
Not primary data or systematic review

2. 1. 4 Assessment of Applicability to the Inclusion/ Exclusion Criteria for the Literature Search

The electronic literature search produced 2032 articles. After an initial manual screening of titles and abstracts, 1893 articles were excluded as they were either duplicates or did not adequately met the inclusion/ exclusion criteria for the literature search (table 2. 1). A further manual screening of the remaining 139 articles produced seven articles that met the inclusion/ exclusion criteria and seemed to provide an opportunity to confirm the theoretical basis for this area of enquiry.

Although a substantial proportion of the rejected articles reviewed for relevance focused on pregnant women with depression, it was often within the context of broader management strategies regarding antenatal care. Where pharmaceutical intervention was incorporated, the excluded papers included other antidepressants besides SSRIs. When SSRIs were included in the articles, it was detailed within the broader management of depression not specifically in the pregnant population, or the outcomes concentrated on other known consequences such as NAS and PPHN, rather than a prolonged QT interval itself. Where a prolonged QT interval was the focus, it was either not specifically in the context of antenatal exposure, or not specifically with SSRI usage, and therefore these papers were not retained.

Among the seven papers that resulted from the review of the remaining full text articles, there were two literature reviews (Courtney, 2009; Tuccori et al, 2009), a systematic review (Fenger-Grøn et al, 2011) and an article response (Dubnov-Raz et al, 2010). These four papers, whilst including pregnancy and neonatal outcomes when SSRIs were used antenatally, only referenced retained primary papers with regard to the neonatal QT interval, and therefore were excluded. The references of those seven articles were also reviewed, and one further literature review was

ascertained (Ray et al, 2014). This final literature review did not add to the knowledge base or provide any unknown primary papers, and so was also excluded (Ray et al, 2014). Whilst the literature reviews, the systematic review and the article response did not contribute to knowledge on the research question, they did corroborate the lack of other evidence regarding the effects of SSRI exposure on the neonatal QT interval published before 2005. These five papers are briefly discussed in section 2. 2. 4. Three final papers were therefore retained and are summarised below (table 2. 2), with a more comprehensive summary in appendix F.

Table 2. 2 Table Summarisation of Retained Articles from Literature Search

Authors	Title of Article	Research Design	Setting/ Cohort
Degiacomo J and Luedtke S (2016)	Neonatal Toxicity from Escitalopram Use in Utero: A Case Report	Case study	Texas. NICU A nine-hour old exposed infant. Day 2 ECG- QT=531 msecs
Dubnov G, Fogelman R and Merlob P (2005)	Prolonged QT Interval in an Infant of a Fluoxetine Treated Mother	Case report	Israel Term exposed baby. Murmur on exam. ECG at 30 hours old. QT=540-580 msecs
Dubnov-Raz G, Juurlink D, Fogelman, R, Merlob, P, Ito S, Koren G and Finkelstein Y (2008)	Antenatal Use of Selective Serotonin Reuptake Inhibitors and QT Interval Prolongation in Newborns	Case- controlled study - retrospective	Israel. 52 exposed to SSRIs v 52 not. >/= 35/40. ECG mostly day 1-2. Controls had heart murmur-> ECG. QT = > 460 msecs in 5/52 exposed v 0/52 not. QT= > 440 msecs in 6/52 exposed v 1/52 not.

2. 2 Literature Review

The research methodology of the retained papers was low in evidence quality ranking. The gold standard, a randomised controlled study, was not evident in this literature review (section 3. 1). This literature search encompassed all design methods and therefore highlighted two case studies (Degiacomo et al, 2016; Dubnov et al, 2005) and a case- controlled study (Dubnov-Raz et al, 2008) that were considered to have met all the inclusion criteria and therefore could potentially provide a theoretical basis for the topic of enquiry and empirical data for future research. These papers are reviewed in the following sections.

2. 2. 1 Critical Analysis of the Retained Case-Controlled Study

The study by Dubnov-Raz et al (2008) was carried out in a large tertiary unit in Israel. This appeared to follow on from an earlier case study (Dubnov et al, 2005) which was also retained in the literature search (section 2. 2. 2). Whilst it was standard care to do ECGs in the study environment, the Dubnov-Raz et al (2008) study undertook a retrospective review of the ECGs that occurred between 2000-2005, and the associated patient notes. Neonates with antenatal exposure to SSRIs received an ECG within the first few days of life, but primarily on day one and two. The study randomly matched those neonates with antenatal SSRI exposure to unexposed, neonates with a heart murmur, who subsequently had a normal echocardiogram, but who were comparable for gender and gestation. The ECGs were retrospectively reviewed by a Paediatric Cardiologist blinded to SSRI exposure. The study found an association between antenatal SSRI exposure and a prolonged QT interval. Five of the 52 neonates in the case group had a pathologically prolonged QT interval when assessed against three standard deviations from the mean (> 460 milliseconds), as opposed to none of the 52 neonates in the control group (p=0.057). The results were further assessed against the widely accepted European Society of Cardiology QT interval standard of > 440

milliseconds (Schwartz et al, 2002) and six of the neonates in the case group had a QT interval of at least two standard deviations from the mean, against a background of one neonate in the control group ($p = 0.02$). All QT intervals in these infants had normalised when an ECG was repeated up to one year of age.

The Dubnov-Raz et al (2008) study reported a significant finding when >440 milliseconds was used as the abnormal QT value, but this result needs to be interpreted with caution considering the small sample size involved, and no odds ratio or confidence intervals being stated in this study. However, the clinical significance of six out of 52 neonates in the case group having a prolonged QT interval versus only one in the control group warrants a cautious approach with regard to clinical care when there has been antenatal SSRI exposure.

The clinically significant, greater incidence of prolonged QT interval in the antenatal SSRI exposed group demonstrated in the Dubnov-Raz et al (2008) study is considerable, however, this was a case-controlled study which has the potential to overestimate risk (Yonkers et al, 2014). A case -controlled study only has the ability to show an association, it cannot therefore demonstrate causation (Yonkers et al, 2014). This study had only small sample size of 52 in each group, so how representative and generalisable the research findings are to the wider neonatal population is unknown. The study also included late preterm infants (35 weeks gestation and above) who potentially could exhibit greater physiological variation in the QT interval and therefore could compound the association seen in the study (Ulrich et al, 2014).

The control group in the Dubnov-Raz et al (2008) study were neonates who were unexposed to SSRIs but underwent ECG screening as part of investigations for a heart murmur, so potential for underlying pathology to affect the results should be acknowledged. Three of the five neonates with a prolonged QT interval in the case group, had been exposed to paroxetine, with the other two being exposed to

fluoxetine. Since the FDA reclassified paroxetine as a Category D drug when used in pregnancy, its use has decreased, so the negative association noted in this study may not be replicated with the currently used SSRIs (Charlton et al, 2015). The study stated the groups were randomly matched, but they were not matched by the time the ECG occurred. 80% of the case group and 40% of the control group had ECG screening on day one and two, with the rest occurring on day three. The QT interval is variable in the first few days of life, so the potential impact of carrying out ECGs at less than 48 hours of age on the study's results should also be acknowledged (Schwartz et al, 1982).

Further, the Dubnov-Raz et al (2008) study provided no evidence of controlling for confounders such as depression or patterns of SSRI use in pregnancy. Case notes were used to retrospectively assess the participants, yet these are unreliable and prone to bias if incorrect or incomplete, and there was no cross- checking with prescription services or the women themselves regarding SSRI use in pregnancy (Udechuku et al, 2010; Wichman et al, 2009). Finally, the demographics of the study population were not reviewed to highlight other potential confounders.

2. 2. 2 Critical Analysis of the Two Retained Case Studies

The two case studies focus on two different SSRIs, fluoxetine (case study one - Dubnov et al, 2005) and the newer escitalopram (case study two -Degiacomo et al, 2016) (table 2.1 and 2. 2). The case studies were reported 11 years apart, and the prolonged QT interval was an incidental finding when the neonates presented with a heart murmur. Both had normal echocardiograms and serum urea and electrolytes, and there was no family history of long QT syndrome, so other potential pathology was excluded. Case study one was based in Israel, where it is standard practice for neonates exposed to any maternal medications to undergo a medical examination, ECG and blood chemistry screening (Dubnov et al, 2005). Unlike the neonate in case study one, the neonate in case study two, showed severe signs of SSRI toxicity, with admission to the neonatal unit, respiratory

distress and seizures (Degiacomo et al, 2016). The QT interval of both case study neonates took a few days to normalise, with the neonate exposed to antenatal escitalopram not having a normal ECG finding till day 11 of life (Degiacomo et al, 2016; Dubnov et al, 2005).

As SSRIs were introduced in the 1980's and ECG screening was standard care in case study one (Dubnov et al, 2005), any potential effect from exposure to SSRIs should have been noted previously in other neonates. No other previous cases of prolonged QT in the neonate from antenatal exposure to SSRIs were reported in case study one (Dubnov et al, 2005).

The prolonged QT interval was first noted in both case study neonates on day one-two (Degiacomo et al, 2016; Dubnov et al, 2005) when that parameter is variable (Schwartz et al, 1982), and therefore may not have reflected a true finding. The persistence of a prolonged QT interval in both neonates, gives credence to the presentation on day one- two, but also demonstrated a transient nature of the effect, with the normalisation of both QT intervals in the neonatal period, that is before 28 days of age (Degiacomo et al, 2016; Dubnov et al, 2005).

Whilst not reflecting a quality research methodology standard, these papers reflect clinical scenarios suggesting a practice- based association between SSRIs and a prolonged QT interval. Single case reports can only be used as a tool for highlighting concerns that larger studies can then expand upon in a more methodologically appropriate way (Koren et al, 2012). Here an earlier case report demonstrated a potential association between an SSRI and a prolonged QT interval (Dubnov et al 2005), which could have been the impetus for the Dubnov-Raz et al (2008) study.

2. 2. 3 Other Considerations

Amongst the retained papers, two had the same lead author (Dubnov et al, 2005; Dubnov-Raz et al, 2008) which highlights expertise in the topic area, but also the potential for author bias. This dominance of the subject area by one researcher and his colleagues, and indeed amongst those papers latterly excluded (section 2. 2. 4), highlights potential bias in generalisability to the wider neonatal population, and the need for further good quality research to explore a possible association between antenatal use of SSRIs and a prolonged neonatal QT interval.

Only English language papers were retained as funding was not available for translation services. This may have led to the potential bias from the exclusion of non-English language papers, however as the references of the three retained articles and those of the four detailed in section 2. 2. 4 elicited no studies in other languages, this seems unlikely.

This extensive literature search was limited to 2005- 2018, which may have potentially excluded any earlier papers. However, the review of the references in the retained papers and a repeat literature search on Delphis (restricted to 1980- 2004), did not produce any earlier papers relevant to the research question.

2. 2. 4 Papers that Met the Search Criteria but Provided No Primary Data and So Were Excluded

The four literature/ systematic reviews (Courtney, 2009; Fenger-Grøn et al, 2011; Ray et al, 2014; Tuccori et al, 2009) were excluded as they only referenced the papers by Dubnov et al (2005) and Dubnov-Raz et al (2008) without adding any additional primary data.

The systematic review by Fenger-Grøn et al (2011) which examined paediatric outcomes following intrauterine exposure to SSRIs, stated that although a prolonged QT interval was observed in their included paper (Tuccori et al, 2009), clinical significance was questionable. This systematic review was however limited to only a PubMed database search, so the limited scope of the papers included suggest there is potential for selection bias (Fenger-Grøn et al, 2011). Indeed, case- control studies were included in the search strategy for this systematic review, but the only article that was referenced in relation to SSRIs was Tuccori et al (2009), meaning data from the Dubnov-Raz et al (2008) study were not directly utilised despite being published at that time (Fenger-Grøn et al, 2011). This review also included serotonin norepinephrine reuptake inhibitors (SNRIs), which whilst SSRI-like in structure and pharmaceutical properties, are not SSRIs, which may have affected the results found.

The Tuccori et al (2009) literature review looked at safety concerns associated with the use of SSRI antidepressants during pregnancy. This literature review stated that the possible association between SSRIs and a prolonged QT interval needed further investigation, however, this review only searched three databases, again leading to a potential selection bias. It also searched specifically for SSRIs from 1966-2009, however SSRIs were not introduced until 1987.

The second literature review looked at the use of antidepressants in pregnancy and stated that SSRIs may cause a prolonged QT interval (Ray et al, 2014). However, this review only referenced the Dubnov et al (2005) case study, and not their case-controlled study (Dubnov-Raz et al, 2008). This emphasised the limitations of this review having not utilised papers higher in the evidence-based hierarchy, and again potential selection bias.

The final literature review was centred on a case presentation of a pregnant woman with depression and her treatment options in the light of available evidence

including effects on the neonatal QT interval, but which did not present any primary data (Courtney, 2009). Finally, the Dubnov-Raz et al (2010) paper was purely an article response, however it did put forward the interesting hypothesis that as serotonin has been indicated in embryological cardiac development, it could potentially be the cause of a prolonged QT interval for some cases.

2. 3 Summary

World Health Organisation (WHO) (2013), in its action plan for the following 14 years, recognised that good quality research is key to improving mental health services. However, this extensive literature search has clearly demonstrated that use of SSRIs in pregnancy and its potential association with a prolonged QT interval in the exposed neonate is lacking in robust good quality research. There is potential for the negative associations described within the three retained papers to have occurred by chance. The number and quality of the papers elicited from this review therefore do not provide a definitive answer for the research topic. Dubnov-Raz et al (2008) has started investigating this research area with a limited case- controlled study, but this gap in knowledge needs to be addressed through further investigation, so that women are fully informed regarding the effect of SSRI exposure on their neonate, and potentially routine ECG screening and surveillance can be implemented for this neonatal group if found to be at a higher risk. This study, based on my clinical role and the literature search results, was therefore developed to answer the null hypothesis that **antenatal exposure to selective serotonin reuptake inhibitors is not associated with a prolonged QT interval in term neonates (37 weeks gestation or greater) when assessed by an electrocardiogram at 48 – 72 hours of age.** In addition, it was anticipated that such a study would demonstrate the pattern of SSRI usage, the range of SSRIs used in pregnancy, maternal mental health problems experienced by the case group women and any unknown associations between the antenatally SSRI exposed and unexposed neonate, and the data collection was structured in order to achieve this.

3 Methodology, Method and Ethical Considerations

The research study, that was devised to address the gap in knowledge and test the stated null hypothesis, is detailed next. The following chapter includes the methodology for the study, in addition to the methods by which the study was carried out, and ethical considerations for the neonate, parents and professionals participating in the study.

3. 1 Methodology

The philosophical underpinning for the study was determined by the deductive approach needed to develop a hypothesis that could be tested by the use of an objective test, the ECG reading (Kawulich, 2012; Polit et al, 2004; Profetto-McGrath et al, 2010). A positivist methodology requires objective, observable and quantifiable results that can be statistically analysed and generalised to the wider world (Kawulich, 2012; Polit et al, 2004; Profetto-McGrath et al, 2010), therefore this study used a quantitative approach which is characteristic of scientific research (Profetto-McGrath et al, 2010) to achieve this. As little is known about the research area, an exploratory, observational study design was utilised for this practice- based research. Positivist methodology require variables to be defined to permit replication and verification by other researchers (Kawulich, 2012), and this standard has been applied to the method of this study.

The FDA, and latterly the National Institute for Health (NIH) recognised the need for robust research involving the pregnant population (Baird, 1999; U.S. Department of Health and Human Services Food and Drug Administration, 2018). An ethical framework therefore set standards of practice including ensuring that the purpose of the research is the attainment of knowledge that cannot be gained from other methods (McCullough et al, 2005; U.S. Department of Health and Human Services

Food and Drug Administration et al, 2018). The gold standard, randomised control trial (RCT), whilst being the most rigorous method of research study is not the only method that can answer a research question. Although randomised control trials are limited for the pregnant population, they have been undertaken for other drug treatment options, such as for the management of antenatal substance misuse to minimise neonatal effects (Jones et al, 2005), however it is inappropriate for this research question. When medication is recommended for the treatment of moderate and severe mental health disorders in pregnancy (NICE, 2014), it would be unethical to be randomised to receive a placebo or behavioural therapy instead, especially when this could potentially lead to maternal and neonatal outcomes similar to untreated exposure as detailed earlier (section 1. 3. 2). Equally, if the control arm of the RCT is a non -SSRI antidepressant, there is potential for other side effects to compromise the fetus and efficacy for the woman may be affected. Mastroianni et al (1999) stated that if research participation is not to meet the needs of the pregnant woman then the risk to the neonate must be minimal, so an RCT would be challenging to devise for this research population.

Other research methods besides a randomised controlled trial therefore needed consideration. A prospective cohort study evaluating all the neonates with SSRI exposure over a period of time to assess whether they developed a prolonged QT interval would not have been appropriate for this research question either. The challenges of following up a family with the potential for a life-threatening event, over a period of time, along with the physical and emotional burden caused by an ECG surveillance programme to ascertain a potential defect, would be challenging to ethically defend. This type of research study would also be very time consuming and challenging to achieve within the timeframe of a doctoral thesis.

Unlike the study location reported by Dubnov-Raz et al (2008), the UK does not routinely undertake ECGs on all SSRI exposed neonates, therefore a

retrospective cohort study where the notes of antenatally SSRI exposed neonates are reviewed for the development of a prolonged QT interval, would need a change to clinical practice or it could have the potential for type II error. This research method would require adequate retrospective data and would be vulnerable to bias from incorrect and incomplete records (Gearing et al, 2006). Alternatively, a retrospective cohort study of all those who have a prolonged QT interval and were born since 1987, could ascertain whether there was antenatal exposure to SSRIs, but this would also be lengthy and prone to bias from incomplete records and maternal recall bias.

Therefore, a case- control research design is the highest feasible research design within the hierarchy of evidence to answer the research question without undue burden on the participants. Drawing on case- control research design, this case - controlled study compared a small sample of individuals with a specific characteristic (exposure to SSRIs in pregnancy), with individuals from as close a population as possible for whom that characteristic was absent (not exposed to SSRIs in pregnancy) to assess the impact of that variable on the neonatal QT interval.

Case- control research design is a useful method for preliminary exploration where limited data have been ascertained about the risk factor incidence in the study population (Mann, 2003), and these attributes also applied to this case-controlled study. Here, data regarding the risk of a prolonged QT interval in the neonate exposed to SSRI use in pregnancy were gained from the only published case-controlled study (Dubnov-Raz et al, 2008), although two case studies had also suggested a potential link (Degiacomo et al, 2016; Dubnov et al, 2005). The null hypothesis of the study stated that there was no association between antenatal exposure to SSRIs and an effect on the neonatal QT interval, so a study design which has the ability to assess an association (Yonkers et al, 2014) is ideal.

Considering the research question, the assessment tool (ECG screening), the research environment, and the number of participants required, utilising the case-

controlled method as demonstrated by Dubnov-Raz et al (2008) was the most scientifically appropriate. This method was therefore considered appropriate for investigating the potential association of the variable, SSRI use in pregnancy, in relation to the presence of a prolonged QT interval in a term neonate at 48 -72 hours of age, in the absence of a randomised controlled trial.

3. 2 Method

Having decided that this research question is best answered through the use of a positivist, methodological framework, the following sections detail the methods by which the study occurred in conjunction with current clinical practice. It describes the recruitment process for both the case and control groups, the inclusion and exclusion criteria for the study and the sample size calculations. Further, it details how data collection occurred via the data collection sheet and the neonatal ECG. Then, the process for interpretation of the ECG data and any further action that was taken is described. The management of the resulting study documentation is defined, and finally the methods by which the results were analysed are explained. This systematic framework provides a robust quantitative method by which data from the sample groups can be obtained and analysed to test the null hypothesis of no association between antenatal SSRI exposure and a prolonged QT interval in the neonate.

3. 2. 1 Background to the Study

The study was scheduled to be carried out at the maternity unit of a District General Hospital where 5,000 births a year occur. The data collection was planned to commence on 17th February 2016 and run for 24 months, thus ending on the 16th February 2018. Collection of data, that is the ECG and data collection sheet data, was intended for the first 18 months and an end date was set for the 17th August 2017. Follow up data collection from infants with abnormalities noted on

their ECG at 48-72 hours old, was planned from 17th August 2017 to 16th February 2018.

The characteristics of the study participants were the subject of great discussion with the supervisory team, and latterly the Ethics Committee. It was decided that following stability of physiological parameters regarding the QT interval, potential case group participants would be neonates who were exposed to SSRIs in pregnancy and who were still in hospital at 48-72 hours old due to a period of observation. Potential control group participants were neonates who were still in hospital at 48- 72 hours as they had a theoretical risk of sepsis but were subsequently found to be healthy. It was recognised that the control group could not be comprised of normal, healthy babies as these neonates could be discharged from hospital from 6 hours of age, and therefore would not be available to have an ECG at 48- 72 hours of age. The neonates within the control study group were exposed to in-utero cefotaxime, metronidazole, clindamycin or tazocin by virtue of maternal treatment for presumed intrapartum sepsis. Subsequently, these neonates received benzylpenicillin, gentamicin or cefotaxime postnatally as part of standard care pathways. None of the intrapartum or postnatal antibiotics that the neonates for the potential control group were exposed to are known to cause a prolonged QT interval. In addition, these neonates demonstrated through negative blood results, clinical examination, and normal physiological measurements, that they had no clinical evidence of sepsis (section 3. 3). This proxy group where there was no indication of a higher risk of a prolonged QT interval was therefore utilised as the control group for this study. The appropriateness of control group was discussed with the Ethics Committee as detailed on page 83 (section 3. 3) and was accepted.

Different professionals would argue that that only the neonate should be classed as the study participant, however for the purpose of this study the participants are considered to be dyadic, and therefore data were collected on both the woman and the neonate. The neonatal data related principally to the primary outcome whereas

the data from the woman contextualised the primary outcome and provided data for the secondary outcomes.

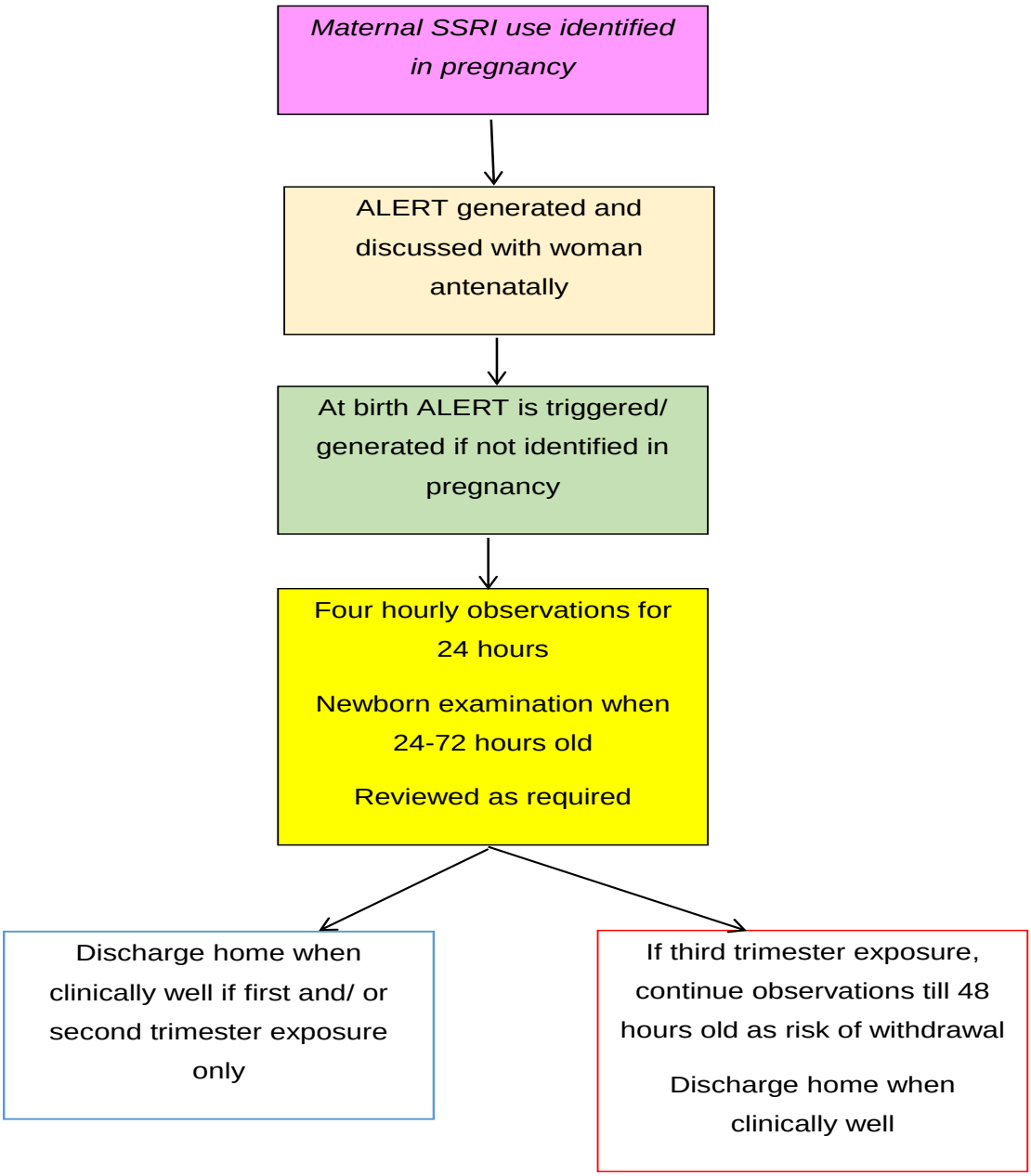
In order to contextualise the research methods, the standard clinical practice that these groups of neonates normally receive needs defining (section 3. 2. 2. 1 and 3. 2. 2. 2).

3. 2. 2 Normal Clinical Practice

3. 2. 2. 1 Normal Clinical Practice for SSRI Use in Pregnancy

It is normal practice for women who take SSRIs in pregnancy to deliver in the maternity unit of the District General Hospital. The neonates born to these women undergo a period of observation as detailed below in figure 3. 1, which necessitates a hospital stay of 24- 48 hours depending on timing of inutero exposure. Most women birthing at the DGH utilise SSRIs for most or all of their pregnancy and therefore follow the right-hand pathway which necessitates a 48-hour hospital stay for observation. With those who have first and second trimester exposure only (left-hand pathway), feeding support often leads to a 48-hour hospital stay even though they have completed their period of observation.

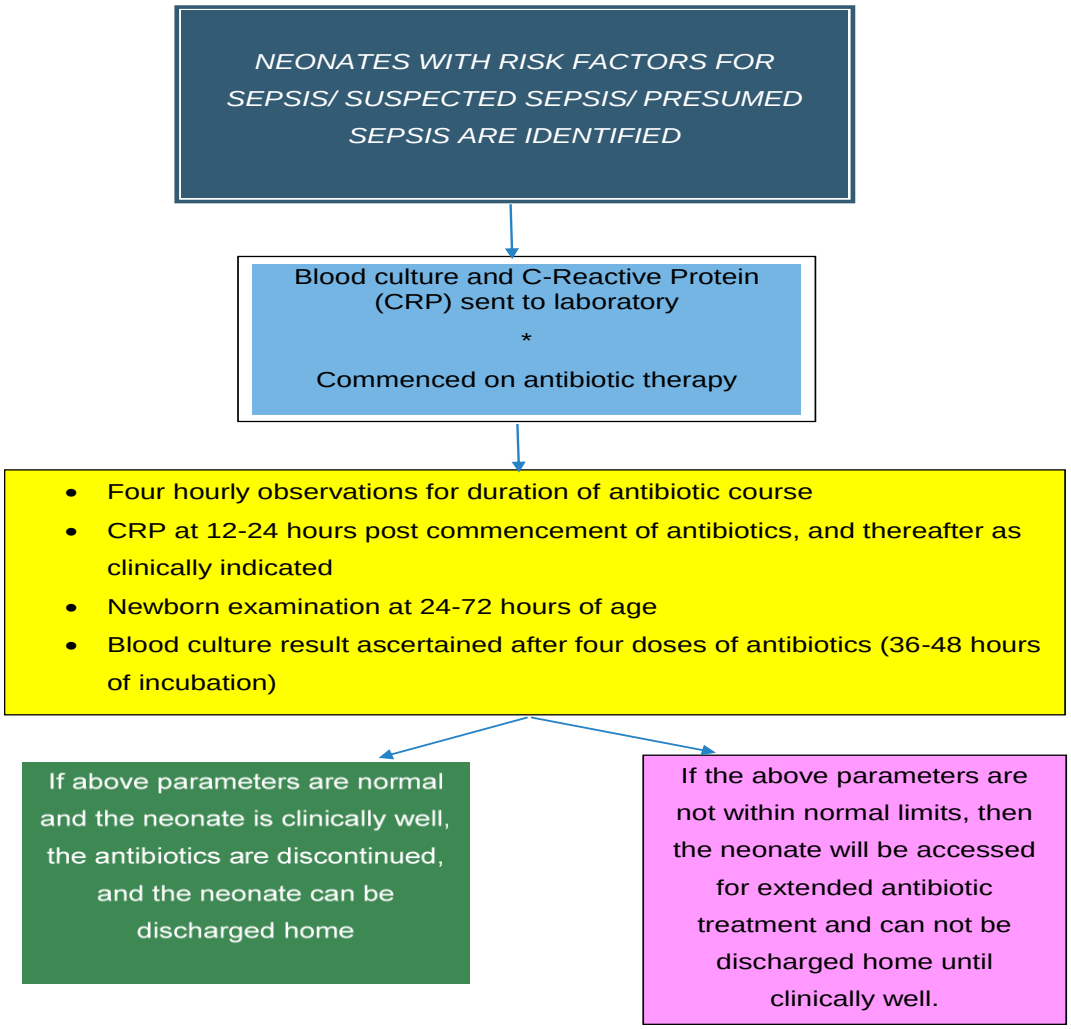
Figure 3. 1 Flow Chart of Standard Care for Antenatally SSRI Exposed Neonates in Study Hospital



3. 2. 2. 2 Normal Clinical Practice for Neonates Being Treated for Sepsis

During their hospital stay, it is standard practice for the neonates being treated for suspected sepsis to be cared for as detailed below in figure 3. 2.

Figure 3. 2 Flow Chart of Standard Care for Potential Control Group Neonates in Study Hospital



The left-hand pathway neonates are labelled as suspected sepsis as no identifiable clinical indicators prove any infection is present. The right-hand pathway neonates are however considered to have presumed sepsis which requires appropriate extended medical treatment. It was the suspected sepsis neonates in the left-hand pathway that formed the potential participants for the control group as they had been shown by a number of parameters to be clinically well with no increased risk of a prolonged QT interval.

Having defined the standard clinical practice for both potential study groups, the next section focuses on the inclusion and exclusion criteria for the study groups.

3. 2. 3 Inclusion and Exclusion Criteria for the Study

The inclusion and exclusion criteria were directed by the research topic, the primary and secondary outcomes, and the use of research papers such as Dubnov-Raz et al (2008). It was key that potential confounders were excluded from the study in order that the results best answered the research question. To this end, exclusion factors involved those aspects that were significant characteristics of the two sample groups. Therefore, to maintain defined study groups, neonates who had antenatal SSRI exposure and those who received treatment for suspected sepsis were excluded from the opposing sample group (table 3. 1 and 3. 2).

Person specific criteria were considered next. Ethical approval required that the parent/ person with parental responsibility was at least 18 years old, and as it was important that the consent was valid, they had to also be clinically well and have capacity to consent (table 3. 1 and 3. 2). They were excluded if this was unable to be established (table 3. 1 and 3. 2). There was no funding for translation services so the parent/ person with parental responsibility had to speak and understand the English language adequately to ensure consent was legitimised (table 3. 1 and table 3. 2).

Table 3. 1 Inclusion and Exclusion Criteria for the Case Group

Inclusion Criteria
37 weeks or more gestation
Age of parent/ person with parental responsibility at least 18 years' old
Healthy parent/ person with parental responsibility with capacity to consent
Healthy neonate
English Speaking parent/ person with parental responsibility
Neonate at least 48 hours' old
Exclusion Criteria
Unable to establish inclusion criteria
Being treated with antibiotic therapy for suspected or presumed sepsis
Maternal cocaine misuse
Maternal methadone use
Maternal use of other antidepressants
Known maternal or fetal structural cardiac abnormality
Neonatal murmur at the time of planned ECG
Congenital abnormalities with a high incidence of cardiac malformations in current pregnancy (e.g., Trisomy 21)
Family history of Long QT Syndrome
Maternal history of SIDS

Subsequently clinical aspects were considered. As there is known variability of the QT interval in the preterm neonate (Ulrich et al, 2014) and in the first few days of life (Schwartz et al, 1982), study participants had to be 37 weeks gestation or greater when recruited to the study and the data collection was not done until the neonates were 48- 72 hours old (table 3. 1). As there were other neonatal pathologies that could potentially affect the new-born's ECG, such as a heart murmur on the newborn examination or neonates born with known or suspected cardiac abnormalities, only clinically well neonates were included in the study (table 3.1 and 3. 2). In addition, any transient neonatal postnatal issues like jitteriness had to have resolved prior to participation in the study. Further, maternal characteristics such as substance misuse, that are known to affect the QT interval were also excluded (Azcert.Org, 2013a) (table 3. 1 and 3. 2, appendix D). Any maternal or family history of QT abnormalities or SIDS also lead to exclusion from the study (table 3. 1 and 3. 2). As this study was

specific to the effects of antenatal SSRI exposure on the neonatal QT interval, any use of other antidepressants in pregnancy also meant those women were not eligible for the study (table 3. 1).

Table 3. 2 Inclusion and Exclusion Criteria for the Control Group

Inclusion Criteria
37 weeks or more gestation
Age of parent/ person with parental responsibility at least 18 years' old
Healthy parent/ person with parental responsibility with capacity to consent
Healthy neonate
English Speaking parent/ person with parental responsibility
Neonate at least 48 hours' old
Exclusion Criteria
Unable to establish inclusion criteria
Maternal cocaine misuse
Maternal methadone use
Maternal use of any antidepressants in pregnancy, including SSRIs
Known maternal or fetal structural cardiac abnormality
Neonatal murmur at the time of planned ECG
Congenital abnormalities with a high incidence of cardiac malformations in current pregnancy (e.g., Trisomy 21)
Family history of Long QT Syndrome
Maternal history of SIDS

Having considered all those women and neonates who would best provide the data to answer the research question, consideration was then given to the number of case and control participants that would be required to demonstrate an association between exposure to SSRIs in pregnancy and a prolonged QT interval in the term neonatal ECG at 48-72 hours old, in the population delivering at the maternity unit of the District General Hospital.

3. 2. 4 Sample Size

Advice was taken from a University of Southampton statistician regarding the sample size required for an 80% power calculation. To undertake the calculation, the study findings of the Dubnov-Raz et al (2008) paper, where the results were assessed against the European Society of Cardiology QT interval standard of >440 milliseconds (Schwartz et al, 2002) were applied to the following calculator to generate a sample size for the study: -

http://www.openepi.com/v37/SampleSize/SSCC.htm

and the results are displayed in table 3. 3. This calculation uses an alpha of 0.05, a beta of 0.2 for a null hypothesis of no association between antenatal SSRI exposure and a prolonged QT interval on the term neonatal ECG at 48-72 hours of age.

Table 3. 3 Statistical Calculation Which Demonstrates the Use of the Sample Size Calculator

Two-sided significance level (%)	95
Power (%)	80
Ratio of sample size, unexposed v exposed	1:1
% of unexposed with outcome	2
% of exposed with outcome	12
Sample size of unexposed	121
Sample size of exposed	121
Total sample size	242

This calculator generated a sample size of 121 in both the case and control group to achieve adequate power, to ascertain whether there was an association between the

two aspects of the research question. This sample size calculation was later manually verified by a second University of Southampton statistician.

Over 12 months in 2014-2015, 119 ALERTS were generated for pregnant women using SSRIs, so allowing for declines, it was decided that the data collection period of the study was achievable within 18 months, at a recruitment rate of 6-7 case group neonates a month. This estimation was comparable with other neonatal studies where the decline rate was between 15 - 36 % (Davis et al, 2007; Ramos et al, 2007) and the local decline rate for research within the maternity unit of 0- 22%. Within a similar review timeframe, 57 babies a month received antibiotics for suspected and presumed sepsis. After exclusion for those neonates who met the presumed sepsis pathway (section 3. 2. 2. 2), there was considerable margin to achieve the average recruitment requirement of 6-7 control neonates a month.

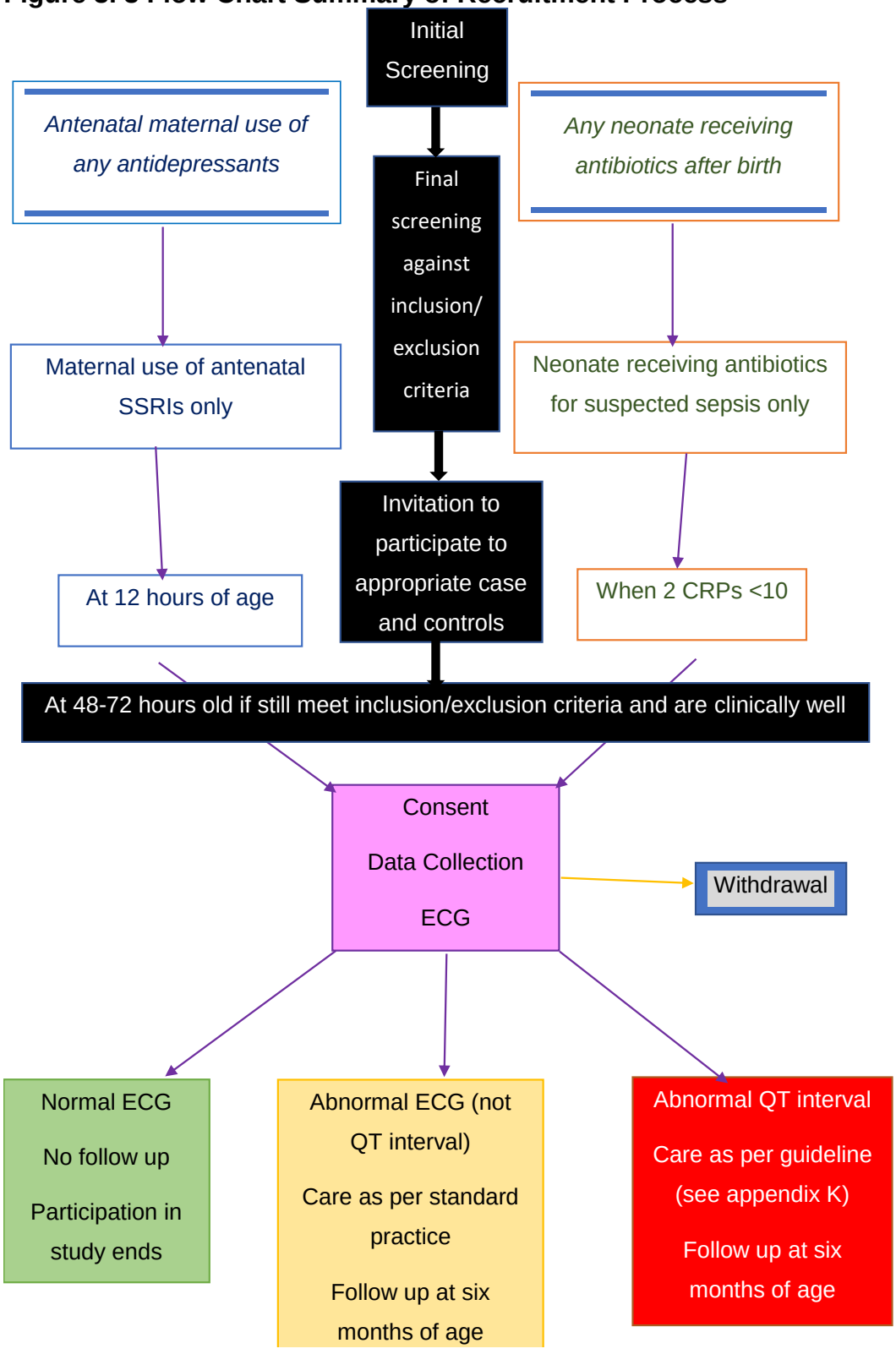
Having defined the case and control groups, the inclusion / exclusion criteria for the study and the sample size required, the following section details the next stage of the recruitment process.

3. 2. 5 Research Study Pathways

My clinical role as the lead ANNP meant that although I would be available to conduct and oversee the recruitment process, I could not feasibly do so for each potential research participant. To this end, I conducted one to one conversations and group presentations with maternity staff and the ANNP team/ Clinical Fellow, so all were aware of the focus of the study, the inclusion/ exclusion criteria and the recruitment process. I repeated this teaching periodically throughout the study so that rotating and new staff were aware of the study and all staff were updated on the process and pathway to be followed.

For ease of recruitment across all staff groups and to minimise impact on clinical care, any woman who had antenatal antidepressant exposure and any neonate who received treatment with antibiotics for suspected sepsis after birth, were notified to myself for consideration for the study. This notification pathway ensured that any potential study participants were highlighted without the need for assessment against the inclusion / exclusion criteria by other staff, whilst minimising potential study losses. A summary of the recruitment process is detailed in figure 3. 3 and in more detail in the rest of this section.

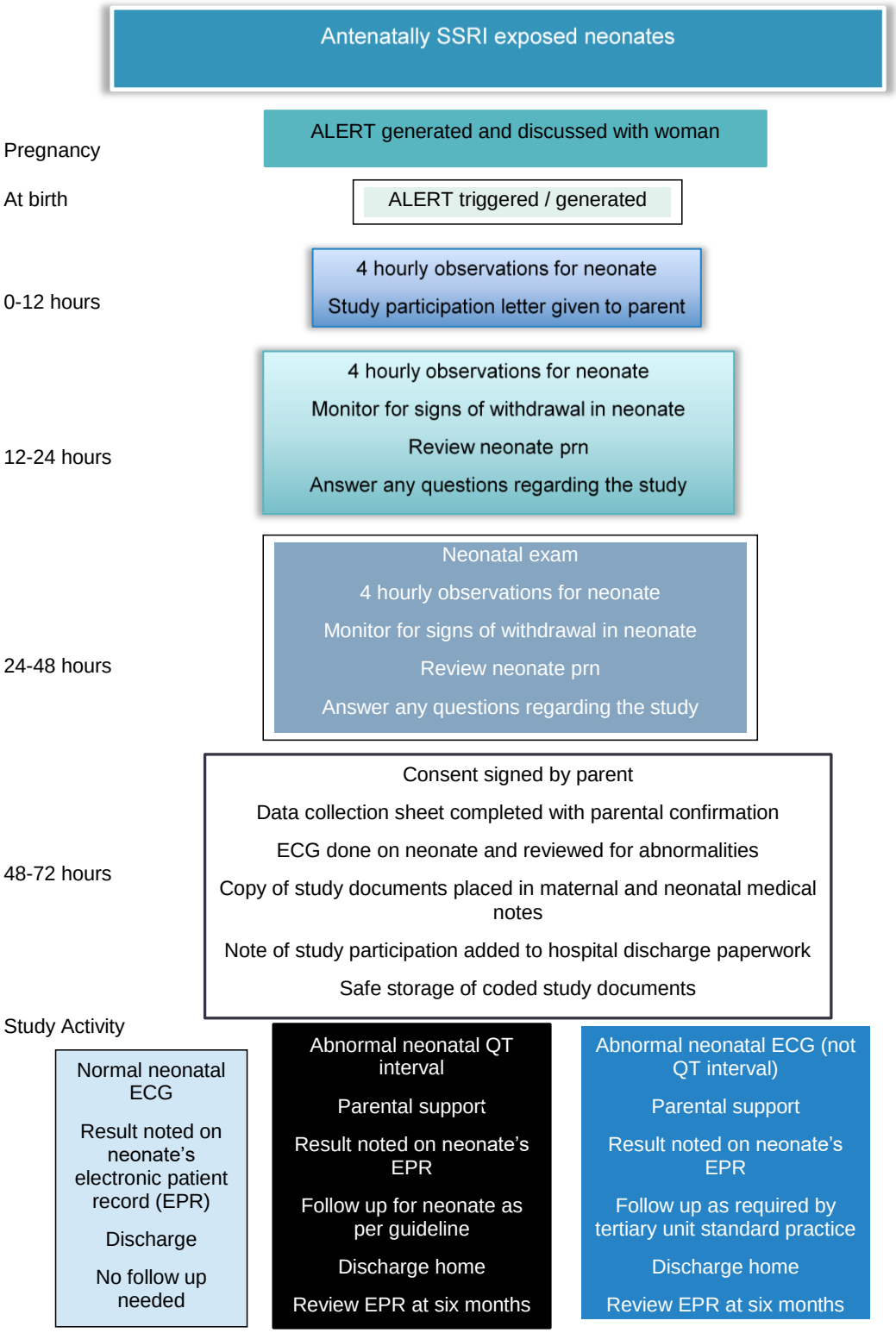
Figure 3. 3 Flow Chart Summary of Recruitment Process



3. 2. 5. 1 Recruitment Pathway for Women Who Utilised Antenatal SSRIs and Their Neonates

When the woman who had taken antenatal SSRIs birthed at the maternity unit, the antenatally- determined plan for postnatal care was triggered (ALERT) (section 1. 3. 6; appendix A). The women who were assessed by myself as meeting the inclusion/ exclusion criteria as detailed in table 3.1 had the study introduced to them 12 hours after birth, and these women & their neonates then followed the research study pathway for case group participants detailed in figure 3. 4 below.

Figure 3. 4 Flow Chart of Research Study Pathway for Case Group Participants

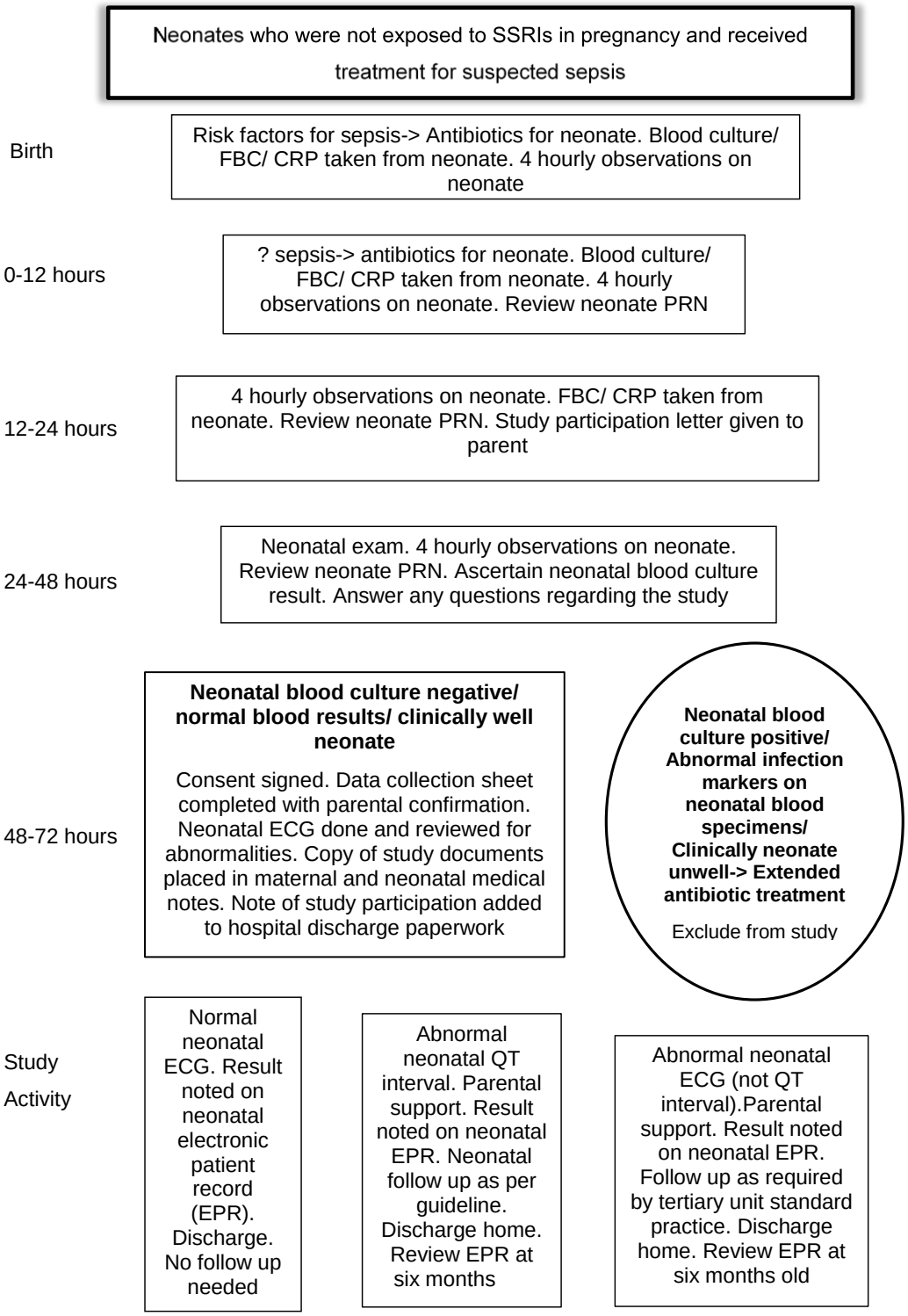


This research study pathway demonstrates the length of time that potential case group women or person with parental responsibility had to consider the study and how the study process was structured around standard clinical practice. The next section highlights the research study pathway for the potential control group participants.

3. 2. 5. 2 Recruitment Pathway for Neonates Who Were Treated for Suspected Sepsis and Their Mothers

Potential control group participants were assessed against the control group study criteria by myself (table 3. 2) once the clinically well baby had two results less than 10mg/l (normal value) of the infection marker, C - reactive protein (CRP), which is routinely monitored for this neonatal population. The women and their neonates then followed the research study pathway for control group participants detailed in figure 3. 5.

Figure 3. 5 Flow Chart of Research Study Pathway for Control Group Participants



It was important that the appropriate potential participants were extended an invitation to take part in the study and this is detailed in the next section

3. 2. 5. 3 Invitation to Participate in the Study

At the appropriate time detailed above in figure 3. 4 and figure 3. 5, an invitation to participate and parent information leaflet (appendix G) were distributed to women who were potential case and control group participants, by a midwife/ ANNP/ Clinical Fellow who had been trained in the research study and process.

In both the case and control groups, the parent/ person with parental responsibility had a minimum of 24 hours to consider participation for their neonate to have an ECG which was not part of standard postnatal care (section 3. 2. 2). During the consideration time, the neonate completed its period of observation as per standard care detailed above (figure 3. 1 and 3. 2). There was opportunity for the parents/ person with parental responsibility to ask the midwifery/ neonatal staff questions regarding the study throughout that period.

Having extended an invitation to participate, the parent/ person with parental responsibility was then approached again when the neonate was 48 hours old to ascertain whether they would be willing to take part in the research study. As potential case and control participants were being approached at the same time, a recruitment strategy for maintaining parity of numbers between the study groups was utilised and is detailed in the next section.

3. 2. 5. 4 Recruitment Strategy to Maintain Parity Between the Two Study Groups

Where practicable, the potential control group participants were the next naturally occurring and appropriate assessed neonate, after an antenatal SSRI exposed neonate had been recruited, so that case and control group numbers were matched within 10 neonates (section 3. 2. 4). When there was 10 neonates' difference between the two groups, the enrolment in the higher recruitment group was halted to allow greater equity.

This recruitment strategy was to allow for seasonal variations in mood, and non-modifiable conditions that may affect a QT interval, such as diabetes, hypothyroidism and epilepsy which were not included in the exclusion criteria, to be equally distributed across the sample groups (Harmatz et al, 2000). When compared to those with a normal glucose profile, those with type 1 diabetes and those with impaired fasting glucose have been found to have a 1.6 times and 1.2 times incidence of a prolonged QT interval respectively (Brown et al, 2001). Those with diabetes have increased T cell abnormalities (King, 2008) and increased levels of cytokines (Felger et al, 2013). Increased levels of cytokines also increase the risk of depression (Felger et al, 2013). SSRIs however reduce the level of cytokines and inhibit T cell production, and in doing so may reduce the potential impact on the QT interval (Adlan et al, 2015). Hypothyroidism alters the autonomic regulation of the heart rate and can cause an increase in ventricular repolarisation and thus cause prolongation the QT interval (Kim et al, 2014). Epilepsy itself does not cause a prolonged QT interval, but congenital long QT syndrome often presents with seizures which are misdiagnosed as epilepsy (Hunt et al, 2005).

Having established a strategy for recruiting appropriately across the two groups, the next stage of the study was the consent process, and this is discussed in the following section.

3. 2. 5. 5 Consent Process

Once time to consider participation had been given, the parents/ person with parental responsibility were asked whether they would be willing to consent for themselves and their neonate to participate in the study by a practitioner, ANNP / Clinical Fellow, who had undergone the District General Hospital's consent training programme. If there was agreement to participate and having ensured that the study process was understood, and any further questions answered, a consent form was completed which confirmed this. The parent/ person with parental responsibility initialled the form to confirm they understood that their participation and that of their neonate was voluntary and later withdrawal from the study would at no time impact clinical care provision or legal rights. They consented to their medical notes and that of their neonate being accessed by the data collection team and relevant outside agencies. The consent form also included permission to access the hospital electronic patient record of the infant at six months of age, to ascertain postnatal outcome for all those with an initial prolonged QT interval or other ECG abnormality. The electronic patient records would provide details of any incidences that required hospital review or admission as part of a paperless strategy by the DGH.

The parent / person with parental responsibility also signed that they agreed to their GP being informed of their participation in the study and the outcome of the ECG for the neonate. The consent form confirmed that appropriate data protection measures would be taken (section 3. 3. 4). Finally, the parent/ person with parental responsibility were asked to indicate whether they would like feedback on the outcome of the study and by what method. The consent forms for the case and control groups are found in appendix H

Having completed the consent form, the next stage of the research process was to undertake the completion of the data collection sheet and the neonatal ECG. This data collection is detailed next.

3. 2. 6 Data Collection for Women and Babies Recruited to the Study

Data collection that occurred in the first 18 months involved the completion of a data collection sheet and a neonatal ECG. Data were only to be included on those recruited to the study and who's neonates underwent a neonatal ECG. These aspects are specified in the following subsections.

3. 2. 6. 1 Data Collection Sheet

When consent was given, the appropriate data collection sheet was then completed using the maternity notes and subsequent verification by the participant. The data collection sheets for the case and control participants are found in appendix I. Completion of the appropriate data collection sheet (appendix I) was undertaken by an ANNP or Clinical Fellow who had successfully completed Good Clinical Practice (GCP) training (section 3. 3. 5) (appendix V) and were aware of the study focus and process. The required information is routinely noted in the maternity notes and included details that the ANNP / Clinical Fellow use regularly to generate neonatal notes. The data collection sheet required details regarding the documented maternal medical history including history of depression, cardiac abnormality, diabetes, epilepsy, hypothyroidism and abnormalities at birth. These details were also acquired for first degree relatives. Maternal alcohol, smoking and recreational drug misuse details were also noted for both groups. Medications taken in pregnancy were noted with a requirement for greater detail regarding SSRIs for the case group. Details of the pregnancy and delivery outcomes were noted as well as details of the neonate with regard to gestation at birth, gender,

weight, postnatal problems, mode of feeding and newborn examination findings particularly cardiac concerns.

This method of obtaining data from the maternity notes minimised the time taken to complete the data collection sheet as the information required was readily available, although details regarding mental health history, SSRI, alcohol and nicotine use needed verbal confirmation. The data collection sheet also provided a useful and practical standardised method by which the case and control group could be assessed for wellbeing and homogeneity outside of the SSRI / antibiotics exposure, and highlighted compliance to the inclusion / exclusion criteria. The data collection sheet enabled the collection of data that could contextualise the QT interval results and the data regarding SSRI use and mental health problems. It also allowed data to be gained on demographics that could potentially affect the QT interval such as diabetes (Brown et al, 2001), age, gender (Manini et al, 2014) ethnicity and alcohol consumption (Rossinen et al, 1999). Additionally, the data collection sheet documented practical aspects of the study such as the timing of the ECG.

Once the consent form and the data collection sheet were confirmed as complete, preparation was made for the neonatal ECG to be done. Until the neonatal ECG was undertaken, the woman and her neonate were not considered to be recruited to the study, so if withdrawal occurred due to parental decision or ECG reading not being obtained, then the data collection sheet and consent form were placed into the confidential waste depository, and no data were retained.

3. 2. 6. 2 Neonatal ECG

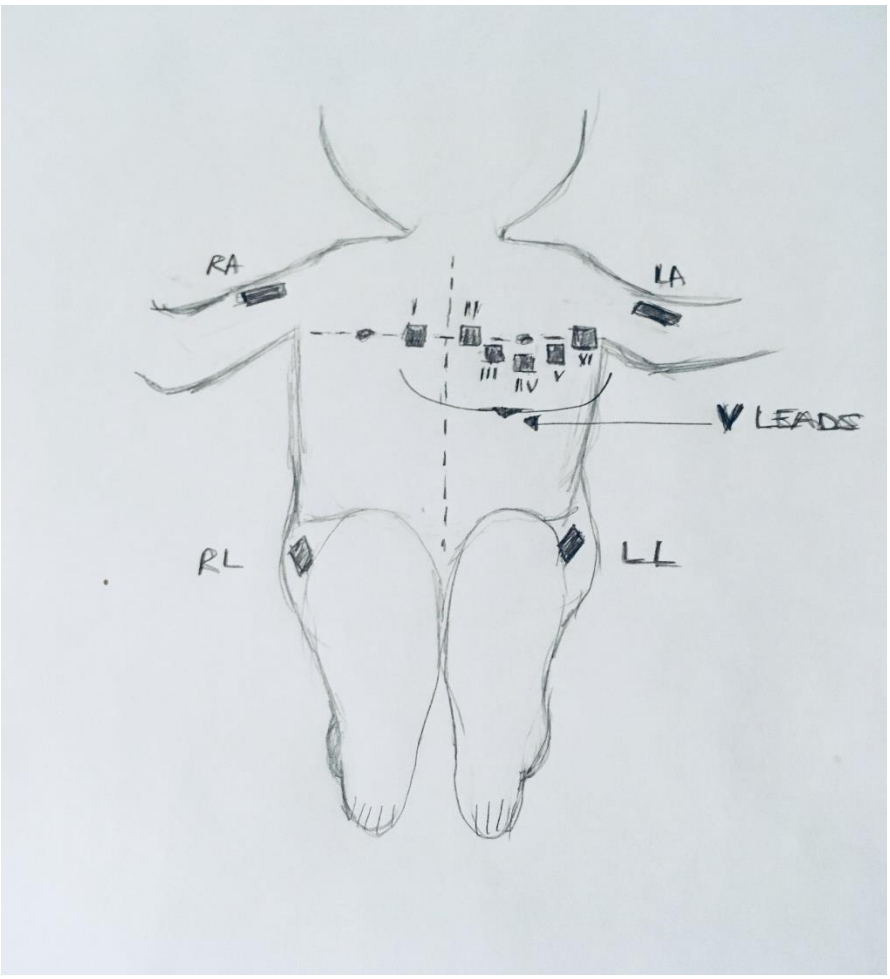
The neonatal ECG was performed at 48- 72 hours old in both groups, and as workload permitted, so occurred at any time of day. Clinical care was paramount, so was prioritised over study participation, however, as a 24- hour ECG service

was offered, a period where it could be undertaken without compromise to care was selected. The maternity unit undertook its own ECG screening service using the Mortara ELI 250 ECG machine which utilises the VERITAS algorithm software developed from the assessment of 5 million ECGs (Mortara Instrument, 2014). The VERITAS algorithm can accomplish complex mathematical assessments and pattern recognition. Its efficacy is such that it is used in drug evaluation and research trials by FDA in the US with specific focus regarding the effects of the drugs on the QT interval (Mortara Instrument, 2014). In 2009, the VERITAS algorithm was enhanced to incorporate paediatric criteria. Thus, when programmed to provide a gender- weight -and- age in days- specific ECG reading, a result with greater sensitivity and specificity is generated. In addition, digital interpretation of the QT interval has been shown to decrease QT interval measurement error and provide improved accuracy, sensitivity and specificity (Meyer et al, 2013). With correct application of the ECG and utilisation of the ECG machine by suitably trained practitioners, false recordings should be minimised.

Those practitioners, including ANNP/ Clinical Fellows/ Maternity Care Assistants (MCA), who successfully complete the hospital's ECG training course undertake the procedure using the Mortara ELI 250 ECG machine as part of routine practice. In addition, each ECG practitioner was further assessed by myself to ensure standard practice and competency to undertake ECGs for this study. The training programme did not include the interpretation of the ECG therefore interpretation was undertaken by the ANNP/ Clinical Fellow/ Neonatal Consultant only. In order to ensure a standard approach for all ECG interpretation, guidance was created (appendix J).

Undertaking an ECG involved placing small sticky pads, electrodes, to the neonate's chest and limbs as demonstrated in the picture below (figure 3. 6).

Figure 3. 6 ECG Lead Placement for Neonates



The electrical impulses of the heart are read via the electrodes and transformed into a graphic interpretation. A trained practitioner undertook the ECG after the neonate has been fed and was content. During the procedure, comforting measures such as containment (placing of hands to mimic the support/ comfort of the uterus) were employed so the neonate remained settled. If the neonate was crying or distressed, the procedure would be delayed or abandoned. The ECG machine automatically selects the optimal 10 seconds of recording within a 5-minute episode, so if the neonate was unsettled a further ECG may not have been necessary. If this was not the case, but the parent/ person with parental

responsibility was still happy to participate and time permitted, the procedure could be attempted again when the baby was settled.

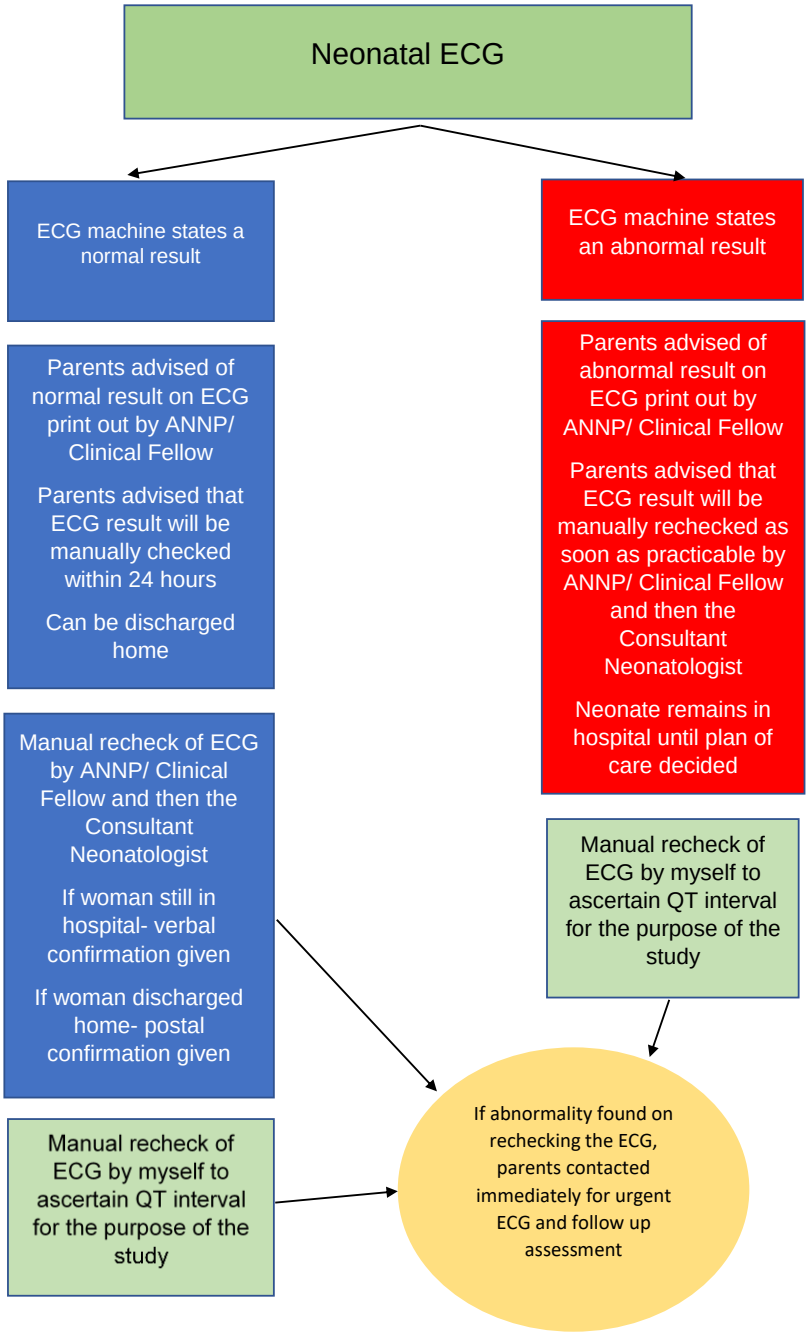
Having undertaken the neonatal ECG for the research study from the neonate, the reading was then assessed for normality and for the presence of QT interval abnormalities (appendix J). ECG interpretation and follow up if there was an ECG abnormality is detailed in the next section.

3. 2. 6. 3 Interpretation of the ECG Result

Having completed the ECG as part of the neonatal data collection for the study, the ECG was presented to the on-call ANNP/ Clinical Fellow/ Neonatal Consultant for interpretation (appendix J). It was within the remit of the ANNP team / Clinical Fellow/ Neonatal Consultant to discuss the results of the reading with the parents/ person with parental responsibility. Figure 3. 7 details the pathway of interpretation for the ECG gained for the study.

If the ECG machine stated the ECG was normal at the time of its undertaking, the parents were informed of the provisional result and the neonate was discharged home pending manual confirmation, as agreed by the DGH Consultant Paediatrician, who served as a link to the tertiary hospital Paediatric Cardiology team. The parent / person with parental responsibility were made aware that it was standard practice for suitably qualified practitioners to manually check ECGs, and that it would occur within 24 hours. The manual reading of the QT interval specifically involved the manually read R R value and the QT value being entered into a QT interval calculator (ECGpedia.Org, 2010) (appendix J). For the purpose of clinical care occurring within this study, the ECG was subsequently checked again by the Neonatal Consultant. If ECG abnormality was found on rechecking the ECG, the parents would be contacted immediately with a request to attend the ECG department for an urgent retest and follow up assessment.

Figure 3. 7 Flow Chart of Interpretation of ECG Pathway



If there was any uncertainty regarding normality of the ECG or an abnormal result was reported by the ECG machine, the parents/ person with parental responsibility were advised immediately that the neonate needed to remain in hospital until the

ECG was formally read by the ANNP/ Clinical Fellow as per current standard practice within the maternity unit (appendix K). For the purpose of clinical care occurring within this study and to confirm the abnormal result, the ECG was subsequently checked again by the Neonatal Consultant. In addition, all ECGs were manually read by myself for the purpose of this study.

Whilst a maximum timeframe of 24 hours was set for review of ECGs classified by the machine as normal, it was as soon as practicable for those with potential abnormalities. Arrhythmias in healthy neonates are rare (De Rosa et al, 2006), but if a prolonged QT interval or other abnormalities were detected on the ECG, support was provided by the ANNP/ Clinical Fellow / Neonatal Consultant. Support for any potential physical or emotional concern falls within the normal remit for these professional groups.

If a prolonged QT interval, that being greater than 440 milliseconds (Schwartz et al, 1998; Schwartz et al, 2002) was manually confirmed on the initial ECG, the guideline detailing the management of prolonged QT in neonates would be followed (appendix K). If other abnormalities were found on the initial ECG, standard care for that abnormality was instigated. When further advice was required, the ECG was reviewed by the Paediatric Cardiology team in the tertiary hospital as is standard practice.

Having completed the neonatal data collection phase of the research process, the final stage of this section of the study was to complete the study documentation. This activity ensured that study participation and outcome was notified to other health professionals and data were logged appropriately. How the study documentation was managed is detailed in the following section.

3. 2. 7 Study Documentation

Documentation for the study involved a consent form (appendix H), a data collection sheet (appendix I), an ECG, the clinical trials participation statement for GCP for the maternal hospital notes (appendix L), a parent letter for result confirmation if they had been discharged prior to manual confirmation of result being known (appendix M), an electronic document for standardised wording for the discharge paperwork on the Medway system (appendix N) as well as standardised wording for the electronic patient record (EPR) (appendix O). The neonatal QT interval result as calculated by myself, and any follow up required was added to the data collection sheet for that participant. The standardised note for the hospital discharge summary documents and EPR were added electronically to notify the GP and primary health care team of study participation and outcome. All study documents were completed, photocopied and stored as detailed in table 3. 4.

Table 3. 4 Study Documentation Completed After ECG Was Undertaken

Study Documentation	Process
Data collection sheet (appendix I).	A photocopy of the data collection sheet was placed in the maternal notes
Consent form (appendix H)	Two photocopies were made. One for the mother to keep and one that was placed in the maternal notes.
Standardised GCP for clinical trials participation wording (appendix L).	Completed and filed in the maternal hospital notes
Manually checked ECG	Photocopied and placed in the baby notes
A standardised note for GP / primary health team (appendix N).	Added to the electronic hospital discharge summary

Study Documentation	Process
A standardised note for all health professional within the local health care setting (appendix O).	Added to EPR
Postal confirmation of the final ECG result (appendix M).	Sent to the parents
All original documentation	Placed in a secure research depository.

In addition to the direct handling of the patient specific documentation, the data generated were also used to populate a log of all women and neonates considered during the initial screening (appendix P), a log of all QT intervals (appendix Q), a spreadsheet detailing the results for the case and control groups, a SPSS database for statistical analysis (appendix R) and a research database which logged outcomes and research activity within the DGH.

To confirm the manually read QT interval results gained as part of the neonatal data collection, a retrospective intra-rater correlation calculator was applied to the study groups. This statistical tool is discussed in the following section.

3. 2. 8 Intra-Rater Correlation Tool

To maintain standards of clinical care for those participating within this study, all the ECGS underwent inter-rater confirmation of the primary result by a Consultant Neonatologist. The manual QT intervals for the study were calculated by myself and to confirm their validity, an intra-rater correlation test was performed as suggested by a University of Southampton statistician. As the primary manual QT interval results for the study were calculated by myself, the intra-rater correlation provided a method to confirm consistency of technique and validity of results. A statistical tool was therefore

used to determine the number of ECGs required to estimate the intra-rater correlations (Bonett, 2002) (table 3. 5; appendix T).

The University of Southampton statistician determined the values to be used in the Bonett intra-class correlation tool that combined scientific validity with practical application. To this end repeated measures (k) was set at two and therefore required one recheck of the nominated ECGs so that two manual QT interval values were obtained for these ECGs (table 3. 5). The intraclass correlation provided a reassurance level that there was 80% certainty of including those with accurately read QT intervals and only a low chance of those that were not (table 3. 5). The desired width of confidence interval provided precision with regard to the number of ECGs reselected. A judgement was made between scientific precision and practical application and a value of 0.2 was selected (table 3. 5).

Table 3. 5 Sample Size Tool for Desired Width- Intra-Rater Correlation Calculation

Repeated Measures	K	2	
Intraclass Correlation (rough estimate)	P	0.8	
Confidence Interval %	A	95	1.959964
Desired Width of Confidence Interval	W	0.2	
Sample	N	?	

To select the actual ECGs for manual recalculation of the QT interval, a true random number generator was used (Random.Org, 2018). The study participant numbers that were generated because of using the random number generator are detailed in section 4. 6. 3 (table 4. 13).

After completion of the data collection phase, there followed a period of assessment for those with abnormal ECG findings. This follow up data collection period is described in the following section.

3. 2. 9 Follow Up Data Collection

It was planned that neonates who had an initial prolonged QT interval and those with other ECG abnormalities would have their electronic patient record accessed at six months of age. This EPR review ascertained the postnatal outcome for all those with ECG abnormalities. The electronic patient records provided details of any incidences that required hospital review or admission within that six- month time frame and provided follow up data for the study (section 4. 10). As there is no suggestion that neonates, exposed to antenatal SSRIs and with a normal QT interval in the early neonatal period, develop a drug related QT interval abnormality in later infancy, there was no requirement to assess those neonates for wellbeing at six months of age. Equally, control group neonates with a normal QT interval at 48-72 hours of age would not be assessed at six months of age.

With completion of the initial and follow up data collection phases, the whole study was concluded within 2 years. Having gained the complete dataset for the study, the data analysis process is detailed next.

3. 2. 10 Methods of Analysis

Statistical analysis was applied to the data gained from the study to assess and validate the outcomes for both research and clinical contexts. The data gathered were entered into the SPSS Statistics Version 22 database (IBM Corp, 2013). There was consistency across each variable and associated coded elements for both the case and control groups in SPSS (IBM Corp, 2013) to ensure reliability of the statistical analysis (appendix R). Family and maternal medical history were grouped by anatomical systems, and significant conditions prioritised for coding in the values

element of the variables (appendix R). Scale data, including birth weight and gestation at birth, were entered in addition to nominal data. As the data were collected prospectively, all data questions were completed fully, however the software was set to detect missing data to confirm this (appendix R). To confirm the number of neonates with a QT interval greater than 440 milliseconds, a targeted variable label was generated where a prolonged QT of greater than 440 milliseconds was equal to one, and a normal QT interval was equal to zero (appendix R).

The IBM SPSS statistical package was used for the final dataset to test the possible association between SSRI exposure in pregnancy and prolonged neonatal QT interval, as well as correlate the demographics and characteristics of the study participants. As the whole data set were expected to follow a normal distribution, that is the QT interval was expected to fall within the normal range for most neonates, a 2-sided confidence interval of 95% was set, with a p value of less than 0.05. The mean, standard deviation and confidence intervals were also calculated where appropriate. Data were rounded to 2 decimal places, unless it was statistically inappropriate to do so. Any significant outcomes that resulted from the statistical analysis were denoted with an asterisk (*).

The Independent Sample T Test was used for the statistical analysis where the data were numerical, such as the data relating to the neonatal QT intervals, the age the neonates had the ECG, in addition to the gestation and birthweight of the included neonates at birth. Cross tabulation was used to examine the frequency distribution between sets of categorical data such as maternal medical history, as well as maternal drug and alcohol use. A form of Chi-squared test, the Fisher's Exact Test, was used where small sample size required analysis such as when analysing maternal ethnicity. Pearson's Chi-Square Test was used to assess the likelihood that differences between categorical data occurred by chance and where

sample size was greater than five, and was applied to the data related to mode of delivery and gender of neonate.

As the FDA highlighted citalopram as being particularly culpable in prolonging the QT interval in adults and especially women (Medicines and Healthcare Products Regulatory Agency UK, 2011; Vieweg et al, 2012) further analysis was undertaken to assess whether there was any significant difference between the neonatal QT intervals of those who were exposed to citalopram in pregnancy and those exposed to other types of SSRIs.

This section has detailed the method by which the study was undertaken. However, it is important that ethical concerns relating to these vulnerable women and babies were addressed, and these are detailed in the next section (section 3. 3).

3. 3 Ethical Considerations

Ethical considerations were discussed at length with the supervisory team, as the study involved two very vulnerable populations, neonates and women with mental health problems, as well as new mothers undergoing their own physical and emotional transition. This led to strategies for managing ethical considerations as detailed in the following sections. This study underwent University of Southampton peer review and was approved on 8th October 2015. After this, the study was submitted to the South West- Exeter Research Ethics Committee for review. The Research Ethics Committee discussed the design of the study and the characteristics of the case and control group. It was acknowledged that the control group were a proxy group, and accepted that treatment for suspected sepsis would not mean an increased risk of a prolonged QT interval in the neonate (section 3. 2. 1). The normal care pathways and how the study protocol linked to normal clinical practice were

discussed. It was accepted that the women using SSRIs in pregnancy would be aware of the potential effects of the medication on her fetus/ neonate, and that no new information would be imparted as part of this study. The study documentation was also assessed for compliance to ethical standards. Amendments and clarification were made as requested, and ethical permission was granted on 16th December 2016 (appendix S). The following sections detail the ethical considerations raised by the Ethics Committee and those that arose from supervisory team discussions for all the key areas of the study including the neonate and the parent/ person with parental responsibility.

3. 3. 1 Ethical Considerations Relating to Parent/ Person with Parental Responsibility

Key issues raised during the South West- Exeter Research Ethics Committee interview focused on the needs of vulnerable women and their neonates. As the ALERT system (section 1. 3. 6) at the DGH provides the woman using SSRIs in pregnancy with a postnatal plan of standard care that is discussed with her antenatally by practitioners trained in caring for women and neonates with this exposure, it was concluded that participation in the study would cause minimal emotional distress.

The South West- Exeter Research Ethics Committee requirement to exclude women birthing at less than 18 years old eliminated the addition ethical regulations required for this specific research group who could legally be considered children themselves and removed the necessity to ascertain whether they are “Gillick” competent to consent for their neonate and themselves to participate in this study (Health Research Authority, 2018; National Society for the Prevention of Cruelty to Children, 2018)

An invitation to participate in the study was extended to the potential case group women when their neonate was 12 hours old. The study could have been introduced antenatally as an adjunct to the ALERT postnatal plan of care for the case group participants, however a great deal of information regarding lifestyle choices, health and parenting is distributed during pregnancy, and it is a period of great change and often highly emotive. By delaying invitations to participate until the postnatal period as detailed in section 3. 2. 3. 1, the study was considered having had confirmation that some potential anxieties were unfounded, whilst not compounding the overload of information that occurred in pregnancy. The postnatal approach did however limit the amount of consideration time the case group participants had, to a minimum of 24 hours. This amount of consideration time was considered appropriate by professionals based on their experience of seeking consent for clinical care, and other research projects, and was accepted by the Ethics Committee.

An invitation to participate in the study was extended to the potential control group women when their neonate had two CRPs <10mg/l. The invitation to participate could have however been extended when antibiotic therapy was commenced. However, encountering potential clinical abnormality where normality was presumed could produce high levels of anxiety. Inviting participation for a study which was not specifically relevant to them at that emotive time would have been inappropriate. Instead deferring the invitation until the neonate had two CRP results within normal parameters and therefore deemed unlikely to have an infection, was considered in the best interest of the potential control study participants and their parents, as well as for optimisation of study recruitment (section 3. 2. 3. 2).

A further concern was that there was the potential for a delay in discharge from hospital due to participation in the study. However, this concern was addressed by

detailing how the discharge process allowed a couple of hours margin, whilst hospital discharge paperwork was prepared and transport home organised, in which the completion of the data collection sheet and ECG could occur without impacting on time of discharge. This continued to be the situation throughout the data collection period, however there was some impact on recruitment as some women still believed that participation would impede discharge despite reassurance to the contrary (section 4. 3. 1). In addition, the control group neonates who started antibiotics late in the evening often remained in hospital overnight pending confirmation of a negative blood culture result when the microbiology laboratory opened in the morning, which again allowed a margin of time to achieve study participation without impact on discharge.

The Ethics Committee were provided with assurance that there was an emphasis on study participation being voluntary during the discussion with the parents / persons with responsibility and in the parent information leaflet (appendix G). This approach was maintained by all the professionals during their interactions with the potential participants throughout the data collection period. If agreement to participate in the study was given, but later retracted, withdrawal occurred without detriment to care, as happened with one participant detailed in section 4. 4. 2.

3. 3. 2 Ethical Considerations Relating to the Neonate

UK consent processes specific to the neonate were employed (Allesee et al, 2011; Allmark et al, 2003) and further sanctioned by the South West- Exeter Research Ethics Committee. Adherence to this guidance was important as the study included neonates, who by virtue of their age, were unable to give informed consent for their own participation in the research.

As the study involved the use of a non-invasive screening tool (ECG) with neonatal comforting measures applied (section 3. 2. 4. 2), it was accepted by the Ethics Committee that the impact on the neonate from participating in the study, was minimal. Further the Ethics Committee were reassured that the procedure involved anti-allergic gel pads with no known adverse effects from use. The ethical considerations assessed the risk: benefit to both the neonate and the parents. As risk was deemed to be minimal, there was no requirement for the neonate to receive direct benefit from participation (Department of Health, 2009; General Medical Council, 2018), although parental reassurance of a normal ECG or detection of an abnormality in the neonate conferred some benefit.

3. 3. 3 Other Clinical Ethical Considerations

The Ethics Committee (appendix S) and latterly the Research and Innovation Department of the DGH who approved the study on the 30th December 2015 (appendix U), were also reassured that normal clinical care would not be affected by engagement of the maternity ward staff and the ANNP team with the study. Clinical care was always the priority and the study process was only undertaken by clinical staff other than myself, when there was an opportunity to do so that would not be detrimental to those being cared for in the maternity unit. This compliance was demonstrated by the numbers of potential participants who were not approached again, after an invitation to participate was extended, due to clinical workload being prioritised (section 4. 3. 1 and 4. 3. 2). Although as Chief Investigator and Principal Investigator, I was allocated 7.5 hours a month to undertake data collection activity, time off outside of clinical duties was utilised to achieve the bulk of the practical and administration aspects of the study process, so clinical care was not affected at that time.

3. 3. 4 Administration Ethical Considerations

Whilst the study was given ethical permission in 2016, the methods for maintaining confidentiality and safe storage of participant data met the General Data Protection Regulation (GDPR) (Information Commissioner's Office, 2018) principles for protecting research participants from information risks and were detailed for both the Ethics Committee and the DGH. As per GDPR principles, enhanced security protection included anonymisation of documents (Information Commissioner's Office, 2018), password protection for the computer used to correlate the data, coding, and locked systems for data storage (section 3. 2. 6). The physical data is stored within a locked cabinet, which is situated within a room with a coded door. This locked room is situated within a limited access ward environment. There are two keys to the locked cabinet which are stored separately within another room with a coded door, and this room is situated in a different limited access ward environment. The documents of those whom were withdrawn from the study were placed in the confidential waste depository located within a room with a coded door and also situated in a limited access ward environment. This level of safekeeping was maintained throughout the data collection, subsequent analysis period for the resulting anonymised data and for the writing of this thesis. Once this study data is no longer required as part of this academic process, it will be secured in the University of Southampton's ePrints depository for a period of 10 years as per University policy (University of Southampton, 2018). Hospital records, including the photocopies of the study documentation, were securely scanned on to the EPR system after discharge and thereafter are accessed via a password protected web page, on a password protected computer. Once scanned the maternal notes were destroyed in a secure location and the neonatal hospital records, including a photocopy of the study ECG, are stored off site in a secure environment that also complies with information governance principles, for a period of 21 years as is standard for neonatal notes.

3. 3. 5. Professional Ethical Considerations

All staff undertaking data collection completed the GCP programme and the Consent in Paediatric Research course provided by the National Institute for Health Research and were therefore aware of ethical principles and correct process for research studies (appendix V). Compliance to these principles was monitored by myself as Chief Investigator and Principal Investigator, and appropriate advice given on maintaining standards as set out by GCP.

3. 4 Summary

This chapter has detailed the methodology that underpins this study. Further it described in detail the process by which the study was undertaken, including screening, invitation to participate, informed consent, data collection, and the safe storage and processing of the data gained. Finally, it reflected on the ethical considerations for the parent/ person with parental responsibility, for the neonate, for the staff and for the process.

Having gained approval from the University of Southampton (appendix W; appendix X), the South West- Exeter Research Ethics Committee (appendix O), the DGH Research and Innovation Department (appendix U) and the neonatal unit manager (appendix Y), the study commenced recruitment as detailed in section 3. 2. 3. The following chapter details the results of undertaking this study according to the method stated in section 3. 2

4 Results

4. 1 Introduction

The study was conducted between 17th February 2016 and 16th February 2018. During this period, a total cohort of 6620 women had live births at the DGH. Data gained from these women and their neonates, utilising the method and methodology stated in section 3. 2, are detailed to answer the null hypothesis that there is **no *association between antenatal exposure to selective serotonin reuptake inhibitors associated with a prolonged QT interval in term neonates (37 weeks gestation or greater) when it is evaluated on an electrocardiogram at 48 – 72 hours of age.***

Information on the total birthing cohort is provided, before the demographics of the women recruited to both case and control groups are presented in order to demonstrate equivalence between the groups chosen. Data related to the primary outcome regarding neonatal QT interval are presented for the neonates who were recruited to the study, the reasons those who consented to participation in the study but were later withdrawn are reported, and outcomes for those who had non- QT interval ECG anomalies are presented. Secondary outcomes regarding the pattern of SSRI usage, the range of SSRIs used and maternal mental health problems amongst the women recruited to the study, are then detailed. Finally, there is an exploration of the data obtained regarding pregnancy and neonatal outcomes to assess whether any unknown associations between the groups are evident. It is important to note that the data analysis throughout this chapter was based on a small sample size with 45% power and there is potential for Type I and Type II errors in interpreting the data.

4. 2 Recruitment

4. 2. 1 Ease of Recruitment Notification

The ease of recruitment process (section 3. 2. 5) meant that 179 women with any antenatal antidepressant use, and 390 neonates being treated with antibiotics for suspected sepsis after birth, were notified for consideration in the study. These 569 women and neonates were then screened against the study criteria to ascertain whether they should be invited to participate in the study, and this is detailed in the next section. This screening was within the context of the recruitment strategy to maintain parity between the two groups within 10 women and neonate pairs (section 3. 2. 5. 4).

4. 2. 2 Screened Women and Neonates

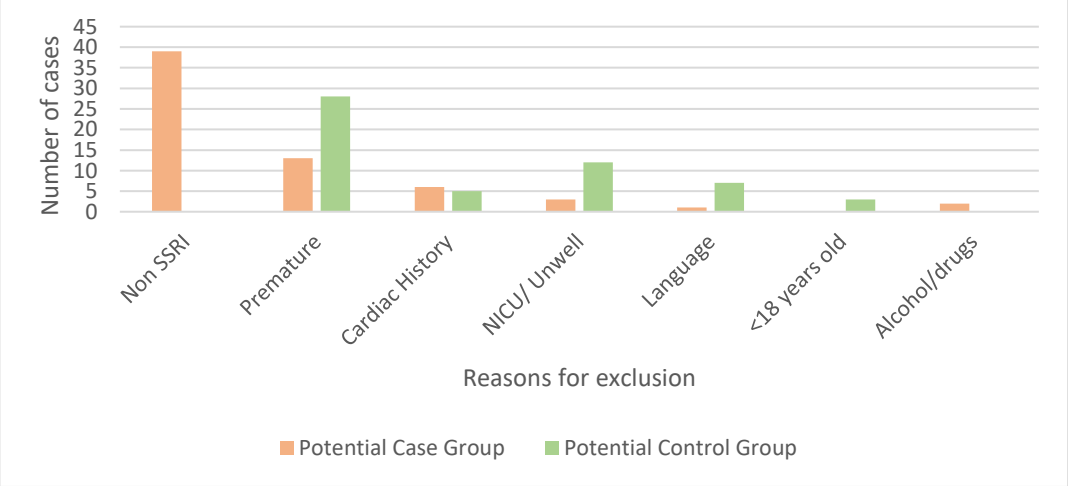
4. 2. 2. 1 Potential Case Group Women and Neonates- Antenatal Antidepressant Exposure

When screened against the case group criteria, 64 women and neonate pairs were not eligible for recruitment to the study:- 39 neonates had been exposed to non-SSRIs antenatally, 13 neonates were preterm, six had a family history of cardiac disorders, two neonates had been exposed to excessive alcohol and substance misuse, three neonates were admitted to the neonatal unit at birth, and language difficulties meant one mother was unable to consent to participation in the study (figure 4.1 and 4. 2). This meant that 115 pairs met the criteria for recruitment to the case group study (figure 4. 2).

4. 2. 2. 2 Potential Control Group Women and Neonates- Neonates Receiving Treatment with Antibiotics for Suspected Sepsis After Birth

When screened against the control group criteria, 55 women and neonate pairs were not eligible for recruitment to the study: - 28 neonates were born preterm, five had a family history of cardiac disorders, 12 neonates were admitted to the neonatal unit around birth, three women were under the age of 18 years old, and language difficulties meant seven women were unable to consent to participation in the study (figure 4.1 and 4. 2). This meant that 335 pairs met the criteria for recruitment to the study control group (figure 4. 2).

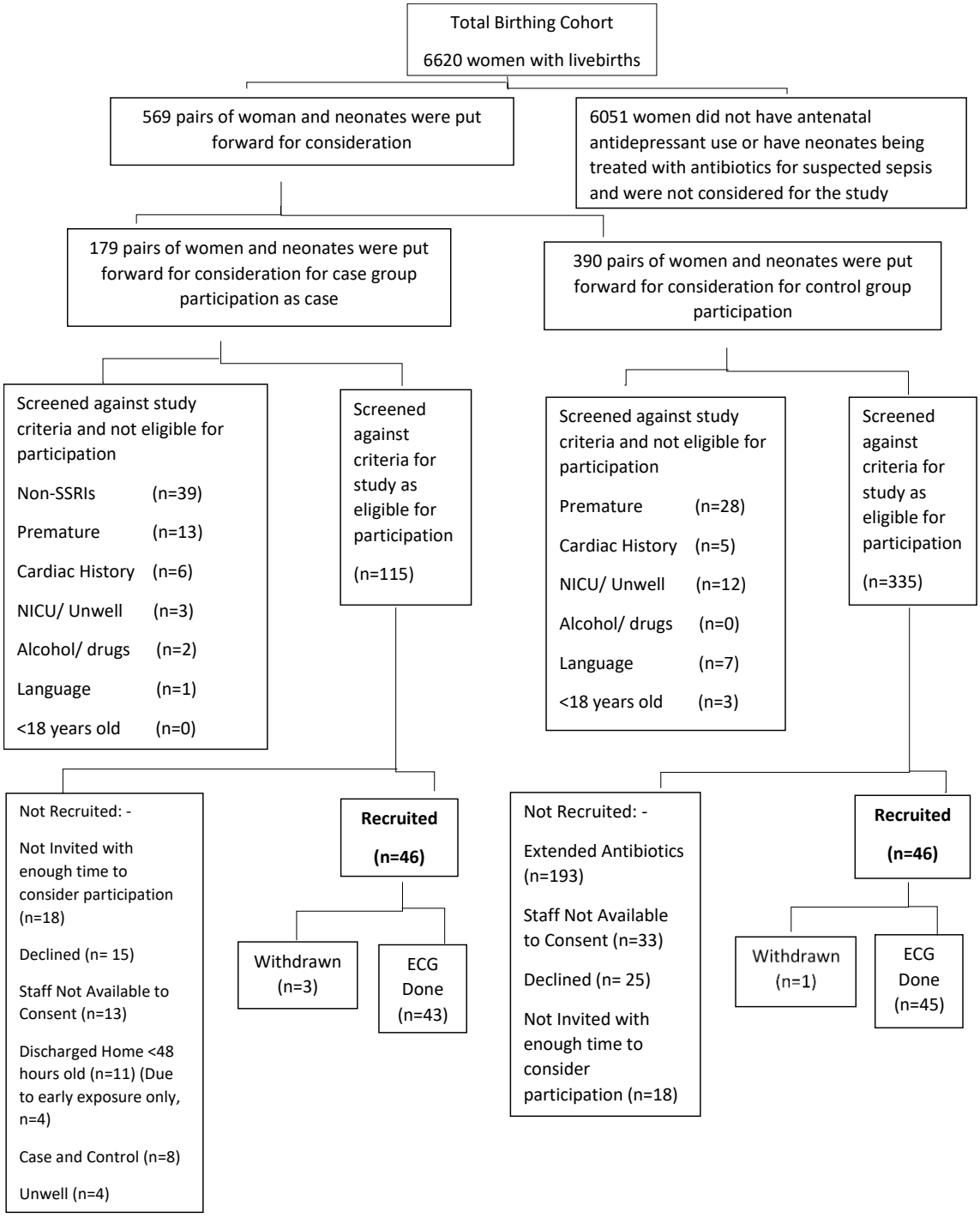
Figure 4. 1 Reasons for the Exclusion of Notified Women and Neonates



4. 3 Recruitment Outcomes for Those Who Met the Criteria for the Study

In total, 450 pairs of women and neonates were screened against the criteria for the study and were considered appropriate to receive an invitation to participate. 115 met the case group criteria and 335 met the criteria for the control group. The recruitment outcomes for these potential participants is summarised in the flow chart below (figure 4. 2).

Figure 4. 2 Flow Chart of All Women and Neonates Who Were Screened for the Study



4. 3. 1 Recruitment Outcomes of Screen Positives for the Case Group

Of the 115 who met the criteria for the case group, 46 were recruited to the study. Due to prioritisation of clinical care, 18 women were not invited to participate in the study within the time frame that allowed a minimum of 24 hours consideration time as required by GCP and the Research Ethics Committee. 15 women declined participation after they were informed of the study. Clinical workload prevented staff from initiating the data collection process for 13 screen positives within the appropriate timeframe, and these women and neonates were discharged from the hospital having not been approached again.

Eight of the neonates initially met the inclusion criteria for the case group as they had antenatal exposure to SSRIs but were excluded after birth as they commenced treatment for suspected sepsis. These eight neonates were therefore omitted to prevent potential overlapping of confounders, which could result in bias in the resulting data. Three neonates and one woman were unwell and therefore were excluded.

Table 4. 1 Recruitment Outcomes of Screen Positives for the Case Group

Recruitment Outcome	Number of screen positives	% of total
Recruited to the study	46	40
Declined participation	15	13
Not invited	18	16
Not recruited to the study	13	11
Early discharge	4	3
Self-discharge	7	6
Suspected sepsis	8	7
Unwell neonate	3	3
Unwell woman	1	1
Totals	115	100

Four women and their neonates were discharged home within 48 hours of birth. There was early pregnancy use of SSRIs which expedited discharge before 48 hours postnatal age, as the neonates were feeding well and there were no other concerns (section 3. 2. 2. 1). Seven other women took self-discharge against medical advice within 48 hours of delivery.

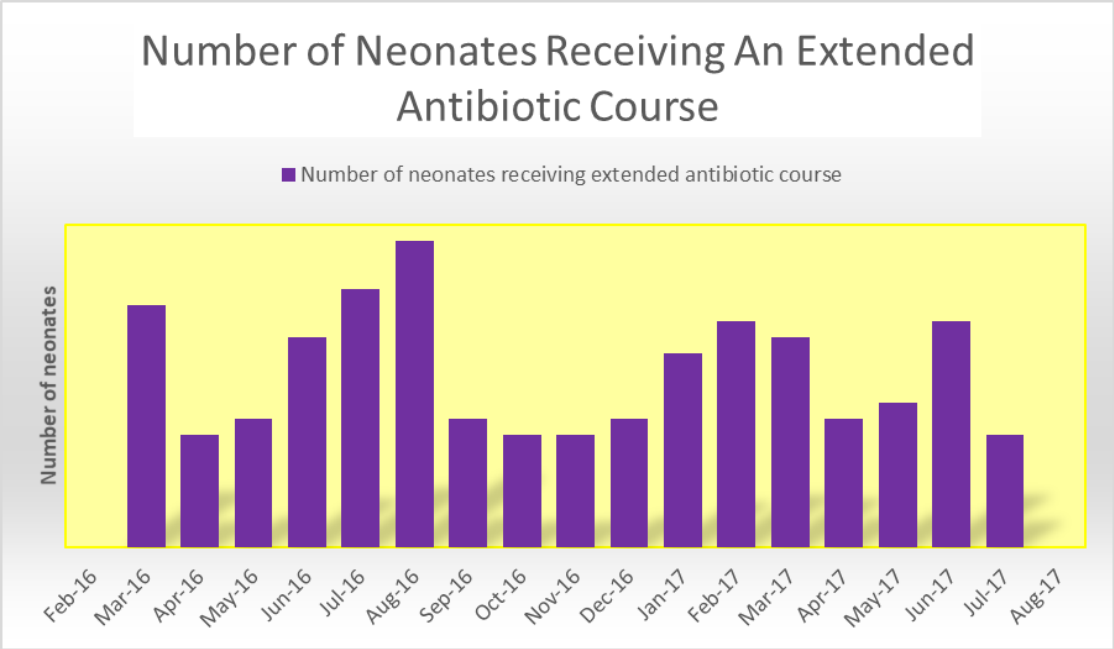
The recruitment outcomes for all the 115 who were screened against the criteria for the case group are summarised in table 4. 1.

4. 3. 2 Recruitment Outcomes for Screen Positives for the Control Group

Of the 335 who met the criteria for the control group, 46 neonates who were treated with antibiotics within 12 hours of birth for suspected sepsis, but were subsequently confirmed as clinically well, were recruited to the control group. Due to prioritisation of clinical care, 18 women were not invited to participate in the study within the time frame that allowed a minimum of 24 hours consideration time as required by GCP and the Research Ethics Committee. 25 women declined participation after they were informed of the study. Clinical workload prevented staff from initiating the data collection process for 33 screen positives within the appropriate timeframe, and these women and neonates were discharged from the hospital having not been approached again.

193 (58%) neonates were excluded as they required extended antibiotic treatment for presumed sepsis. These neonates predominantly had raised serum infection markers that necessitated a prolonged course of antibiotic therapy. As they were clinically unwell, they were not considered for recruitment. The number of neonates that required extended antibiotics was variable across the study timeframe and is depicted monthly in the below figure to demonstrate this variability (figure 4.3).

Figure 4. 3 Bar Chart Demonstrating the Monthly Control Group Exclusions Due to Extended Antibiotic Treatment.



Nine neonates and two women were unwell and therefore excluded from the recruitment process. Nine of those invited to the study, left the hospital before their baby was 48 hours old and therefore were not recruited. This was due to antibiotic therapy being discontinued prior to 48 hours of age, as the blood culture result was available promptly.

Table 4. 2 Recruitment Outcomes of Screen Positives for the Control Group

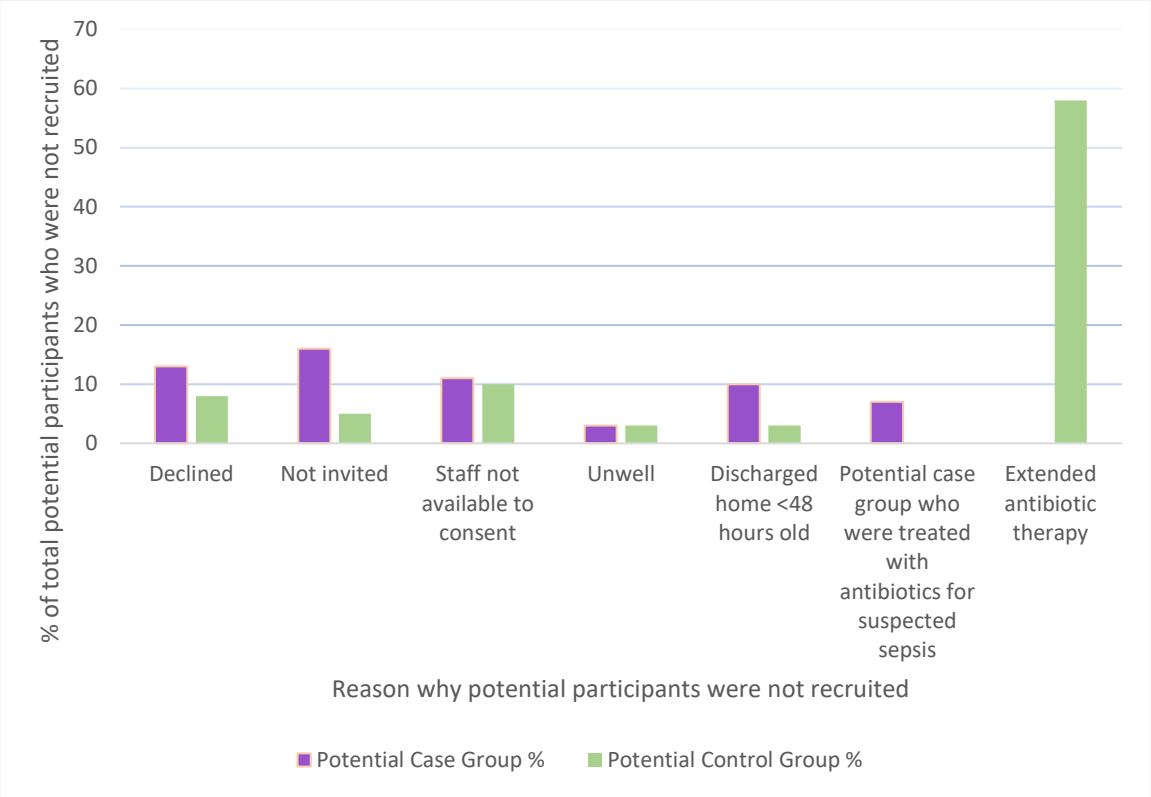
Recruitment Outcome	Number of screen positives	% of total
Recruited to the study	46	14
Declined participation	25	7
Not invited	18	5
Not recruited to the study	33	10
Early discharge	9	3
Extended sepsis	193	58
Unwell neonate	9	2
Unwell woman	2	1
Total	335	100

The recruitment outcomes for all the 335 women and neonates who were screened against the control criteria are summarised in table 4. 2.

4. 3. 3 Comparison of the Recruitment Outcomes of Screen Positives Who Were Not Recruited to Either the Case or Control Groups

Within the case group screen positives, the most frequent reason for not being recruited was due to clinical workload preventing their recognition as study participants within the timeframe that met the requirements for GCP and ethical approval. For the control group screen positives, the most frequent reason for not being recruited to the study was the need for prolonged antibiotic treatment for presumed sepsis. The percentages of potential women or neonates who were unwell or for whom clinical workload prevented recruitment were similar in the two groups. The rate of decline to participate in the study was marginally greater amongst the potential case group participants, and there was a similar trend for discharges before 48 hours of age. The recruitment outcomes for the screened potential women and neonate pairs who were not enrolled despite being eligible are compared in figure 4.4.

Figure 4. 4 Bar Chart Comparing the Recruitment Outcomes of The Screen Positives Who Were Not Enrolled in Either Group



4. 4 Neonates Where Consent Was Obtained to Participate Within the Study

The following section provides information concerning the number of neonates in each study group, where the parent/ person with parental responsibility consented to participation in the study.

4. 4. 1 Neonates for Whom Consent Was Obtained for the Case Group of the Study

- 46 neonates who had antenatal exposure to SSRIs were consented.

- Three of the 46 were consented but later withdrawn. In two cases the ECG machine malfunctioned, and an ECG could not be obtained. In the other case, the neonate became clinically unwell between the time of consent and the ECG being undertaken, so was withdrawn from the study as they no longer meet the inclusion criteria.

4. 4. 2 Neonates for Whom Consent Was Obtained for the Control Group of the Study

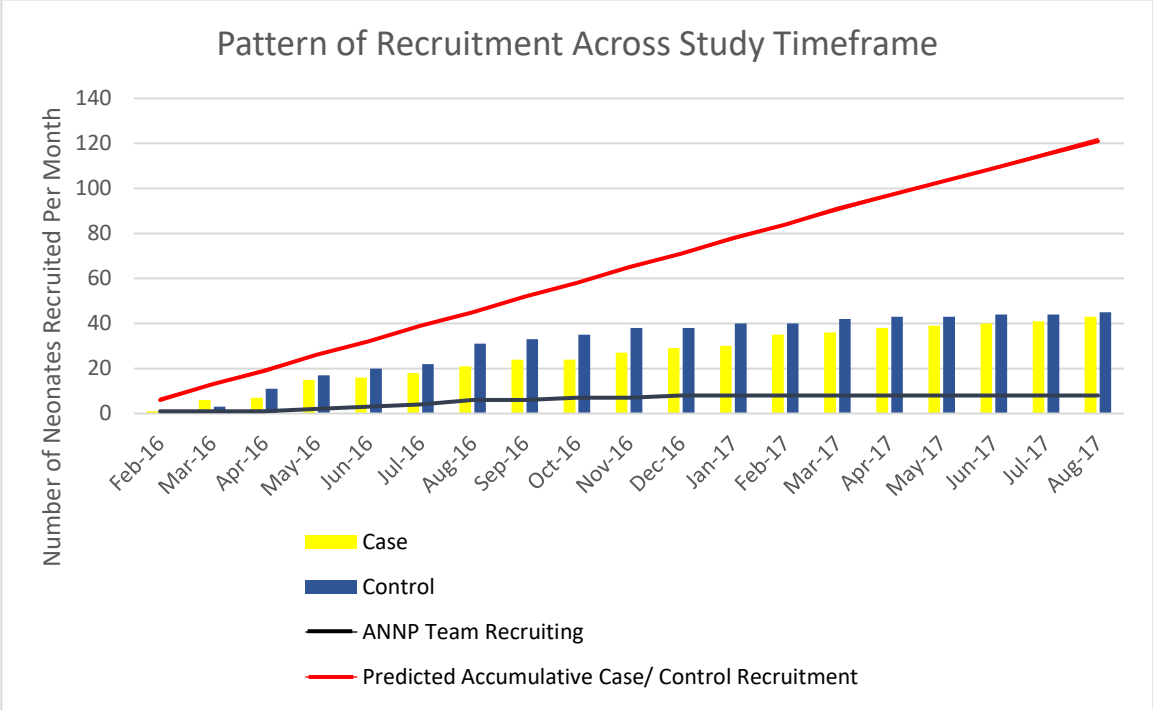
- 46 neonates who were treated with antibiotics within 12 hours of birth for suspected sepsis, but were subsequently confirmed as clinically well, were consented.
- One control group neonate was however withdrawn from the study after consent to participate was obtained. This control neonate had hiccups and a good ECG trace could not be obtained. The mother of this neonate declined a repeat ECG.

4. 4. 3 Pattern of Recruitment Across Study Timeframe

88 neonates were recruited to this study. 40 neonates were recruited in the first six months, 18 were case group neonates and 22 were control group neonates. During this time there was primarily one member of the data collection team completing the recruitment and data collection process. From July 2016 to January 2017, 12 case group neonates and 18 control group neonates were recruited, with the rest being recruited in the final six months of the data collection period (figure 4. 5). After the first six months of data collection there were six staff doing data collection. In total, 43 neonates with antenatal SSRI exposure were recruited to the case group and 45 neonates treated for suspected sepsis were recruited to the control group. The bar

chart below demonstrates the actual recruitment versus the planned recruitment during the 18 months of the study (figure 4. 5). In addition the increasing size of the recruitment team is also plotted over time (figure 4. 5).

Figure 4. 5 Bar Chart Demonstrating the Recruitment Pattern Across the Study Timeframe



4. 5 Demographic Data of Women Recruited to the Study

A summary of the data from the data collection sheets (appendix I) completed in conjunction with the 88 women recruited to the study and its subsequent analysis, is shown in table 4. 3, section 4. 5, 4.7, 4.8 and 4.9. The raw data in SPSS format are available in appendix R.

Table 4. 3 Summary Table of Maternal Demographics

	Case	Control	Total	Fishers Exact Test p value~	Pearson's Chi Square Test p value~	95% CI
Sample Size n=	43	45	88			
Maternal Age in years						
Mean (SD)	32.4 (6.2)	30.6 (5.5)	31.48 (5.86)			30.26-32.7
Maternal Ethnicity n=						
White British	41 (95.3%)	32 (71.1%)	73 (83%)			
Other	2 (4.7%)	13(28.9 %)	15 (17%)	0.004*		
Maternal Smoking Behaviour n=						
Never smoked in pregnancy	30 (69.8%)	41(91.1%)	71(80.7%)			
Smoked at any time in pregnancy	13 (31.2%)	4 (8.9%)	17 (19.3%)	0.015*		
Maternal Alcohol Use n=						
Never drank in pregnancy	37 (86%)	43 (95.6%)	80 (90.9%)			
Drank in pregnancy at any time	6 (14%)	2 (4.4%)	8 (9.1%)	0.152		

	Case	Control	Total	Fishers Exact Test p value~	Pearson's Chi Square Test p value~	95% CI
Maternal Recreational Drug Use n=						
Never used	43(100%)	43 (95.6%)	86 (97.7%)			
Used pre-pregnancy	0 (0%)	2 (4.4%)	2 (2.3%)			
Maternal Medical History n=						
Nil of note	10 (23.2%)	16 (35.6%)	26 (29.6%)			
Diabetes	2 (4.7%)	0 (0%)	2 (2.3%)			
Hypothyroidism	0 (0%)	1 (2.2%)	1 (1.1%)			
Maternal Family History n=						
Nil of note	15(34.9%)	23(51.2%)	38(43.2%)			
Cardiac problems	3 (7%)	2 (4.4%)	5 (5.7%)			
Depression	4 (9.3%)	3 (6.7%)	7 (8%)			
Syndromes	1 (2.3%)	1 (2.2%)	2 (2.3%)			
Maternal Medicines Excluding SSRIs n=						
Nil	4 (9.3%)	7 (15.6%)	11(12.5%)			

	Case	Control	Total	Fishers Exact Test p value~	Pearson's Chi Square Test p value~	95% CI
Anti-emetics (of which there is a risk of a prolonged QT interval)	3 (7%) 2	2 (4.4%) 0	5 (5.7%) 2			

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation n= number

4. 5. 1 Maternal Age of Women in the Study

The mean age of the women in the case group was 32 years and five months compared with 30 years and six months in the control group. The mean age of women in the case group was therefore 23 months greater than the mean age of the control group women (table 4. 3).

Table 4. 4 Maternal Age of Study Group Participants

Maternal Age (years)	Case	Control	All
Minimum Age	22	19	19
Maximum Age	49	42	49
Median Age	33	32	32

The combined case and control group women had a mean age of 31.5 years, with the youngest woman in the study delivering at 19 years of age and the oldest at 49 years (table 4. 3, table 4. 4).

4. 5. 2 Maternal Ethnicity of Study Participants

41 (95.3%) of the case group women were of white, British ethnicity compared to only 32 (71.1%) of the controls. Cross tabulation of the data also demonstrates this difference (table 4. 5). As the resulting numbers amongst the control group included a result of five or less, Fisher's Exact Test was utilised to analyse the data. Based on this sample size, there was a statistical difference regarding the ethnicity between the two groups (p=0.004)(table 4. 3).

Table 4. 5 Cross Tabulation of Data Relating to Maternal Ethnicity

Maternal Ethnicity n (%)	Case	Expected Count^	Control	Expected Count^	All	Expected Count^
White, British	41 (95.3)	35.7	32 (71.1)	37.3	73 (83)	73
Other	2 (4.7)	7.3	13 (28.9)	7.7	15 (17)	15
Total	43 (100)	43	45 (100)	45	88 (100)	88

^ Crosstabulation

4. 5. 3 Maternal Smoking Behaviour, Alcohol and Recreational Drug Use of Study Participants

4. 5. 3. 1 Maternal Smoking Behaviour of Study Participants

30 (69.8 %) of case group women reported they did not smoke in pregnancy in contrast to 41 (91.1%) of the controls (table 4. 3, table 4. 6). Crosstabulation of the data also demonstrates this difference (table 4. 6).

Table 4. 6 Crosstabulation of the Maternal Smoking Behaviour

Maternal Smoking Habits, n (%)	Case	Expected Count^	Control	Expected Count^	All	Expected Count^
Never smoked in pregnancy	30 (69.8)	34.7	41 (91.1)	36.3	71 (80.7)	71
Smoked in early pregnancy	5 (11.6)	3.9	3 (6.7)	4.1	8 (9.1)	8
Smoked throughout pregnancy	8 (18.6)	4.4	1 (2.2)	4.5	9 (10.2)	9
Total	43 (100)	43	45 (100)	45	88 (100)	88

^ crosstabulation

The resulting numbers for the smoking subdivisions were small and therefore not appropriate for statistical analysis. In order to provide more meaningful statistical results, a comparison of smoking at any point in pregnancy versus never smoking in pregnancy was conducted instead (table 4.3). Fisher's Exact Test was utilised as only four of the control group had smoked at any time in pregnancy. These differences did meet statistical significance (p=0.015) (table 4. 3).

4. 5. 3. 2 Maternal Alcohol Use

More cases reported alcohol use in pregnancy than controls, although both groups had high levels of abstinence being 37 (86%) and 43 (95.6 %) respectively (table 4.3 , table 4. 7). However, of those that took alcohol in pregnancy, slightly more cases

(n=5) reported alcohol consumption throughout pregnancy than controls (n=2) (table 4. 3, table 4. 7).

Table 4. 7 Crosstabulation of Data Relating to Maternal Alcohol Use in Study Participants

Maternal Alcohol Usage, n (%)	Case	Expected Count^	Control	Expected Count^	All
Never drank in pregnancy	37 (86)	39.1	43 (95.6)	40.9	80 (90.9)
Drank in early pregnancy	1 (2.3)	5	0 (0)	5	1 (1.1)
Drank throughout pregnancy	5 (11.6)	3.4	2 (4.4)	3.6	7 (8)
Total	43 (100)	43	45 (100)	45	88 (100)

^ Crosstabulation

The resulting numbers for the drinking subdivisions were small and therefore not appropriate for statistical analysis. In order to provide more meaningful statistical results, a comparison of drinking at any point in pregnancy versus never drinking in pregnancy was conducted instead. Fisher's Exact Test was utilised as only two of the control group had drunk alcohol at any time in pregnancy. These differences did not meet statistical significance (p=0.152) (table 4. 3).

4. 5. 3. 3 Maternal Recreational Drug Use

No case group women reported ever using recreational drugs (table 4. 3, table 4. 8). Two of the controls reported previous use, but none reported use of recreational drugs in pregnancy (table 4. 3, table 4. 8). Predictably frequencies for each parameter were similar to expected counts for both groups as substance misuse was an exclusion criterion for both groups (table 4. 8).

Table 4. 8 Crosstabulation of Data Relating to Maternal Recreational Drug Use of Study Participants

Maternal Recreational Drug Habits, n (%)	Case	Expected Count ^	Control	Expected Count^	All	Expected Count^
Never used	43 (100)	42	43 (95.6)	44	86 (97.7)	86
Used pre-pregnancy	0 (0)	1	2 (4.4)	1	2 (2.3)	2
Used in pregnancy	0 (0)	0	0 (0)	0	0 (0)	0
Total	43 (100)	43	45 (100)	45	88 (100	88

^ Crosstabulation

4. 5. 4 Maternal Medical History (Excluding Mental Health History)

Aside from mental health disorders, fewer case group women (n=10) than control group women (n=16) were fit and well (table 4. 3, table 4. 9). Of those that reported medical problems, a greater proportion of both groups (case (n=9); control (n=7)) had pregnancy related problems such as pre-eclampsia, rather than other medical problems such as muscular problems or respiratory problems (table 4. 9). Whilst two case group women were gestational diabetics, none of the

control group women had diabetes (table 4. 3, table 4. 9). No recruited women had a history of epilepsy, and only one control group woman had hypothyroidism compared to none in the case group (table 4. 3, table 4. 9).

Table 4. 9 Crosstabulation of Data Relating to Maternal Medical History of Study Participants (Excluding Mental Health History)

Other Maternal Medical Health History, n (%) $	Case	Expected Count ^	Control	Expected Count ^	All	Expected Count ^
Alcohol problems	1 (2.3)	0.5	0 (0)	0.5	1 (1.1)	1
Allergies	4 (9.3)	2.9	2 (4.4)	3.1	6 (6.8)	6
Diabetes	2 (4.7)	1	0 (0)	1	2 (2.3)	2
GI problems	3 (7.0)	3.9	5 (11.1)	4.1	8 (9.1)	8
Gynaeco-logical problems	3 (7.0)	4.4	5 (11.1)	4.6	8 (9.1)	9
Hypertension	0 (0)	0.5	1 (2.2)	0.5	1 (1.1)	1
Infection	0 (0)	2	4 (8.9)	2	4 (4.5)	4
Muscular problems	7 (16.3)	3.9	1 (2.2)	4.1	8 (9.1)	8
Nil of note	10 (23.2)	12.2	16 (35.6)	12.8	26 (29.6)	25
Pregnancy related problems	9 (20.9)	7.8	7 (15.6)	8.2	16 (18.2)	16

Other Maternal Medical Health History, n (%) $	Case	Expected Count ^	Control	Expected Count ^	All	Expected Count ^
Respiratory problems	4 (9.3)	3.9	4 (8.9)	4.1	8 (9.1)	8
Total	43 (100)	43	45 (100)	45	88 (100)	88

^ Crosstabulation $ Major disorder only noted

4. 5. 5 Family Medical History of Study Participants

There was a low incidence of any family medical history problems across both groups (table 4. 3, table 4. 10). Diabetes (n=7 (case); n=5 (control)) and hypertension (n=5 (case); n=7 (control)) were more prevalent than other medical problems in both groups (table 4. 10). A family history of depression, cardiac problems, and syndromes were reported in four, three and one of the cases and three, two and one of the controls respectively (table 4. 3, table 4. 10). Findings were similar to the data on crosstabulation.

Table 4. 10 Crosstabulation of Family Medical History

Maternal Family History, n (%) $	Case	Expected Count ^	Control	Expected Count ^	All	Expected Count ^
Allergies	1 (2.3)	0.5	0 (0)	0.5	1 (1.1)	1
Cancer	2 (4.7)	1.5	1 (2.2)	1.5	3 (3.4)	3
Cardiac issues	3 (7.0)	2.4	2 (4.4)	2.6	5 (5.7)	5
Depression	4 (9.3)	3.4	3 (6.7)	3.6	7 (8.0)	7

Maternal Family History, n (%) $	Case	Expected Count ^	Control	Expected Count ^	All	Expected Count ^
Diabetes	7 (16.3)	5.9	5 (11.1)	6.1	12 (13.6)	12
Gynaecological problems	0 (0)	0	0 (0)	0	0 (0)	0
Hypertension	5 (11.6)	5.9	7 (15.6)	6.1	12 (13.6)	12
Muscular problems	1 (2.3)	1.5	2 (4.4)	1.5	3 (3.4)	3
Nil of note	15 (34.9)	18.6	23 (51.2)	19.4	38 (43.2)	38
Other	2 (4.7)	1	0 (0)	1	2 (2.3)	2
Pregnancy related problem	1 (2.3)	0.5	0 (0)	0.5	1 (1.1)	1
Respiratory problems	1 (2.3)	1	1 (2.2)	1	2 (2.3)	2
Syndromes	1 (2.3)	1	1 (2.2)	1	2 (2.3)	2
Total	43 (100)	43	45 (100)	45	88 (100)	88

^ Crosstabulation $ Major disorder only noted

4. 5. 6 Maternal Medications Excluding SSRIs Utilised by Study Participants

With the exclusion of SSRIs, the majority of antenatal maternal medications related to pregnancy care and pregnancy related problems such as reflux and nausea & vomiting of pregnancy (table 4. 11). Around a third of all women reported the use of vitamins during pregnancy (table 4. 11). Analgesics were reportedly used by nine of the case and five control group women (table 4. 11). Four case and seven control group women reported no use of medications at all in pregnancy. Whilst a medication that has the potential to cause a prolonged QT interval was reported in two case group women (Chlorpromazine and Ondansetron), the control group women utilised medications without such an association (table 4. 3, table 4. 11). Findings were close to expected crosstabulation counts.

Table 4. 11 Crosstabulation of Data Relating to Maternal Medications Excluding SSRIs

Other Maternal Medications, n (%) $	Case	Expected Count^	Control	Expected Count^	All	Expected Count^
Analgesics	9 (20.9)	6.8	5 (11.1)	7.2	14 (15.9)	14
Antibiotics	3 (7.0)	2.4	2 (4.4)	2.6	5 (5.7)	5
Anti-emetics	3 (7.0)	2.4	2 (4.4)	2.6	5 (5.7)	5
Anti-hypertensives	0 (0)	2	4 (8.9)	2	4 (4.6)	4
Anti-reflux	9 (20.9)	7.3	6 (13.3)	7.7	15 (17.0)	15
Inhalers	0 (0)	0.5	1 (2.2)	0.5	1 (1.1)	1
Iron	0 (0)	0.5	1 (2.2)	0.5	1 (1.1)	1
Medicine for	2 (4.7)	1	0 (0)	1	2 (2.3)	2

Other Maternal Medications, n (%) $	Case	Expected Count^	Control	Expected Count^	All	Expected Count^
diabetes management						
Nil	4 (9.3)	5.4	7 (15.6)	5.6	11 (12.5)	11
Thyroxine	0 (0)	0.5	1 (2.2)	0.5	1 (1.1)	1
Vitamins	13 (30.2)	14.2	16 (35.7)	14.8	29 (33)	29
Total	43 (100)	43	45 (100)	45	88 (100)	88

^ Crosstabulation $ Major medication only noted

This section has presented the demographics of the study women and demonstrated equivalence between the two groups with regard to recreational drug and alcohol use, medical history excluding mental health problems, family medical history and medications taken in pregnancy excluding SSRIs. The case group women are older than the controls, more likely to be white, British and smoke in pregnancy.

In order to contextualise the data analysed for the primary and secondary outcomes that follow in section 4.6 and 4. 7, a summary of the data relating to the participating neonates is provided in table 4.12 with further details noted in section 4. 9.

Table 4. 12 Summary Table of Neonatal Demographics

Demographic	Case n=43	Control n=45	Total	Independent Sample T Test p value~	Pearson's Chi Square Test p value~
Gestation at birth in weeks					
Mean (SD)	39+2/40 (1.34)	39+5/40 (1.37)	39+4/40 (1.36)	0.14	
Gender n=					
Male	25 (58.1%)	22 (48.9%)	47 (53.4%)		
Female	18 (41.9%)	23 (51.1%)	41 (46.6%)		0.4
Birthweight in grams					
Mean (SD)	3330(0.52)	3410 (0.46)	3372 (0.49)		
95% CI	3170- 3490	3270- 3530	3371.9- 3372.1	<0.001*	
Neonatal problems n=					
None	25 (58.1%)	36 (80%)	61 (69.3%)		
Problems postnatally	18 (41.9%)	9 (20%)	27 (30.7%)		
Neonatal Examination n=					
Nil of note	32 (74.4%)	33 (73.3%)	65 (73.9%)		
Defect noted	11 (25.6%)	12 (26.7%)	23 (26.1%)		
Mode of Feeding n=					
Breast	17 (39.5%)	24 (53.3%)	41 (45.5%)		
Artificial	16 (37.2%)	7 (15.6%)	23 (26.1%)		
Mixed	10 (23.3%)	14 (31.1%)	24 (27.4%)		0.69

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation n= number

4. 6 Primary Outcome of the Study

The primary outcome for the study sought to ascertain whether antenatal exposure to SSRIs was associated with a prolonged QT interval in term neonates at 48-72 hours of age. In this study, all 88 neonates across both study groups had a normal QT interval (<440 milliseconds) on an ECG when examined between 48-72 hours of age. In this study, no neonatal QT intervals were prolonged in association with antenatal exposure to SSRIs and all values follow a normal distribution. The following sections examine the QT intervals obtained in greater detail starting with the findings of the intra-rater correlation tool calculation. Following on there is a demonstration of the comparability of the assessment methods used to ascertain the QT interval values in the study, before the values generated from all methods are detailed and analysed.

4. 6. 1 Intra-Rater Correlation Tool Calculation

The Bonett intraclass correlation estimating tool calculated that 51 of the 88 ECGs obtained in the study required intra-rater rechecking to confirm the validity of primary manually confirmed QT intervals (table 3. 5).

To select the 51 ECGs for manual recalculation of the QT interval, a true random number generator was used (Random.org, 2017). This generated the following study participant numbers (table 4. 13).

Table 4. 13 Study Participant Number Selected by Random Number Generator for Intra-Rater Check of Neonatal QT Interval

9	23	21	48	62	19	56	25	15	74
86	11	57	40	50	53	88	66	30	52
1	87	16	84	42	32	29	85	70	5
41	22	60	34	4	54	71	46	75	47
83	69	44	35	31	43	26	81	78	51
58									

The above participant numbers represented 27 cases and 24 controls who were selected for the manual recalculation of the QT interval on their ECG (table 4. 13).

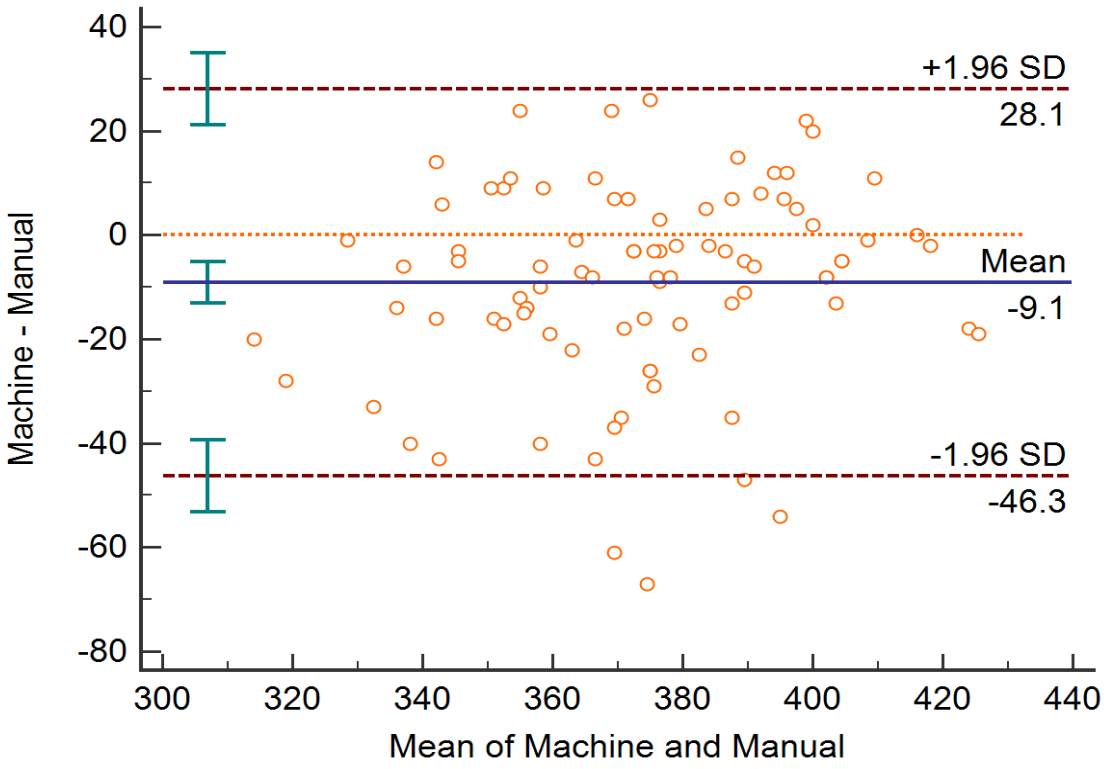
4. 6. 2 Comparison of the Methods of QT Interval Assessment

The QT interval was measured via the ECG Machine and was interpreted manually. The manually confirmed QT intervals also underwent intra-rater correlation testing to confirm the validity of the obtained values. In order to demonstrate the comparability of all the methods used and therefore rationalise the collection and analysis of the data, all methods of QT interval assessment were validated by the use of regression analysis. This statistical process analysed the relationship between the ECG machine generated QT intervals and the manually read QT intervals (figure 4. 6); between the manually read QT intervals and the intra-rater recheck QT intervals (figure 4. 7); and between the ECG machine generated QT intervals and the intra-rater recheck QT intervals (figure 4. 8).

When the QT intervals generated from the ECG machine are compared with the manually read QT intervals through the use of Bland Altman linear regression

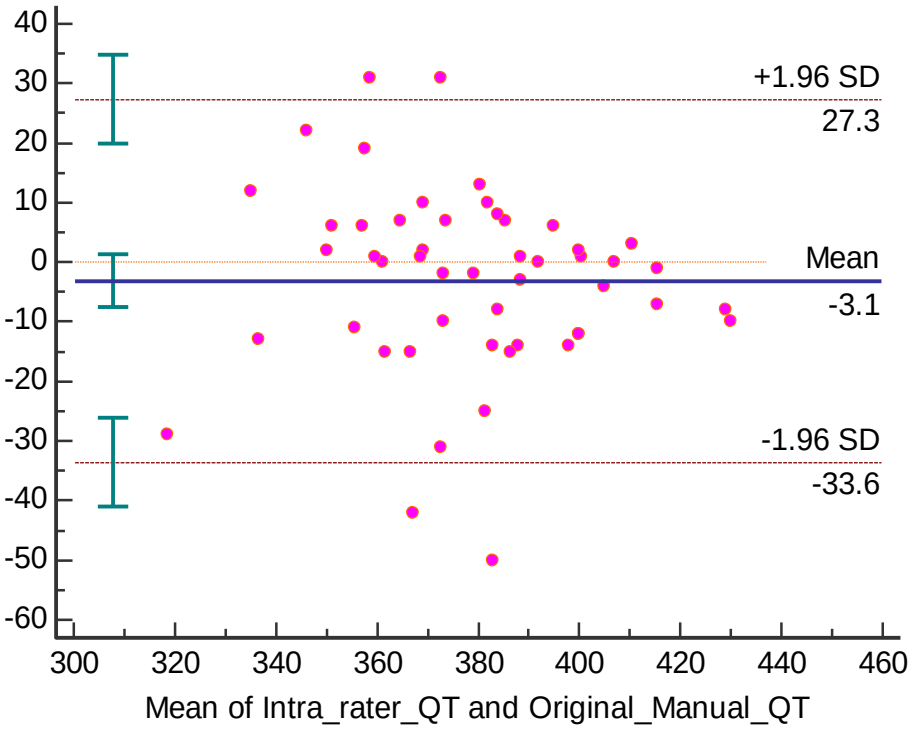
analysis (Bland et al, 2007), the differences between the individual values are utilised to generate the mean and standard deviation. With a 95% limit of agreement set utilising 1.96 standard deviations above and below the calculated mean of the two sets of values, it can be seen that all of the values are less than the upper limit of agreement, the mean plus 28 milliseconds. Although four values are plotted at less than the lower limit of agreement, 46 milliseconds below the mean, this is not clinically significant as QT interval prolongation is under consideration for these study participants.

Figure 4. 6 Comparison of the ECG Machine Generated QT Interval Means and the Manually Read QT Interval Means



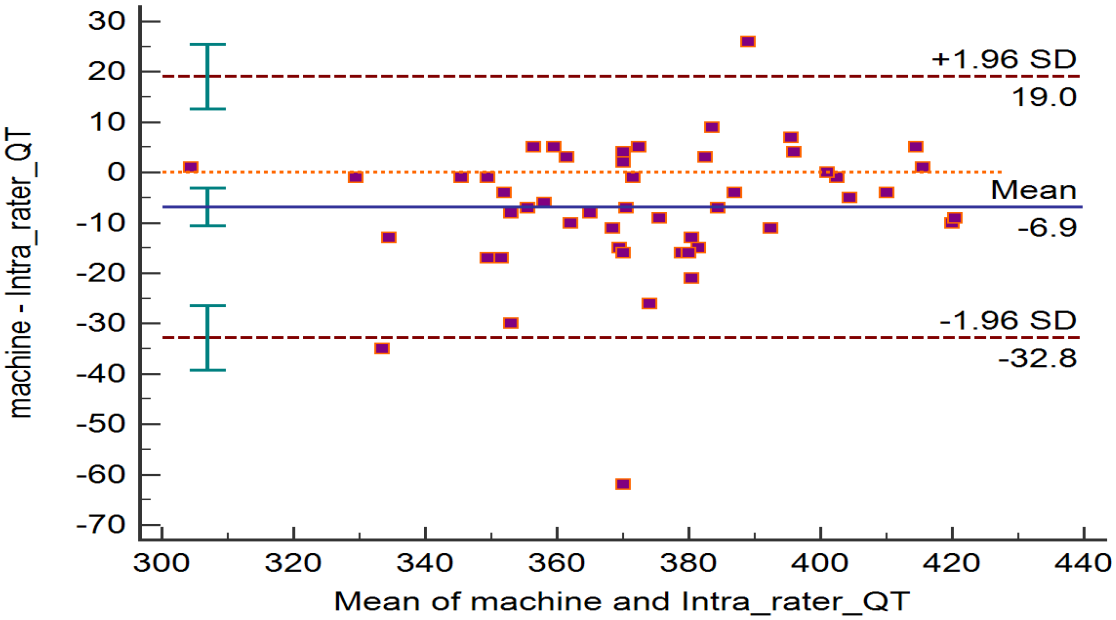
When the manually read QT intervals are compared with the intra-rater recheck QT interval values through the use of Bland Altman linear regression analysis (Bland et al, 2007), it can be seen that most of the values are within the 95% limits of agreement (figure 4.7). With only two exceptions (3.9%), all the values are less than the upper limit of agreement of the mean plus 27 milliseconds.

Figure 4. 7 Intra-Rater Recheck of QT Interval Means for the Chosen Study Participants Compared to Original Manually Calculated Means



When the ECG machine generated QT intervals are compared with the intra-rater recheck QT interval values through the use of Bland Altman linear regression analysis (Bland et al, 2007), it can be seen that most of the values are within the 95% limits of agreement (figure 4. 8). With only one (1.9%) exception all values are below the upper limit of agreement of the mean plus 19 milliseconds.

Figure 4. 8 Comparison of the ECG machine Generated QT interval means and the Intra-rater Recheck QT interval means

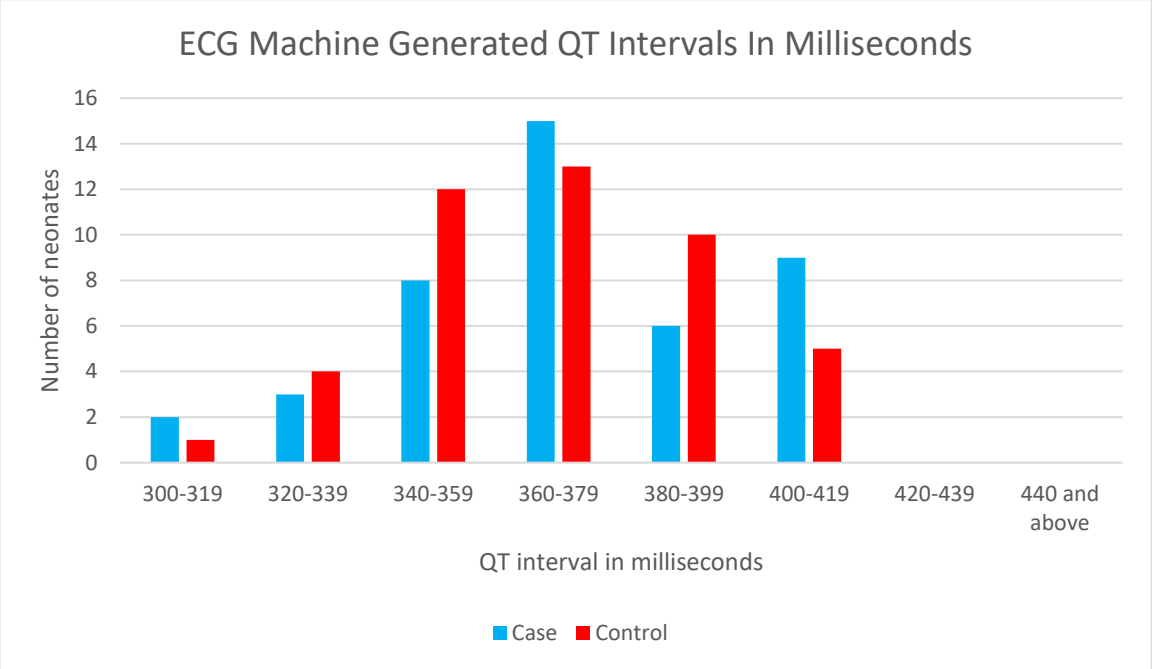


All of the methods used to assess the QT interval have demonstrated that for the most part they are comparable within the accepted ranges of agreement . This analysis is discussed further in section 5. 7. 3, pages 167-168.

4. 6. 3 ECG Machine Generated Neonatal QT Intervals

The mean ECG machine generated QT interval was 369.12 milliseconds (SD= 28.12; 95% CI 360.72- 377.52) for the case group neonates and 368.71 milliseconds (SD= 25.71; 95% CI 361.21- 376.21) for the control group neonates. 74 (84.1%) of all the study neonates had an ECG machine generated QT interval of less than 400 milliseconds (figure 4. 9). The range of QT intervals across both study groups were similar, being 305- 417 milliseconds for the case group neonates and 304- 416 milliseconds for the control group neonates. There was no statistically significant difference between the two study groups regarding ECG machine generated QT intervals (p= 0.943).

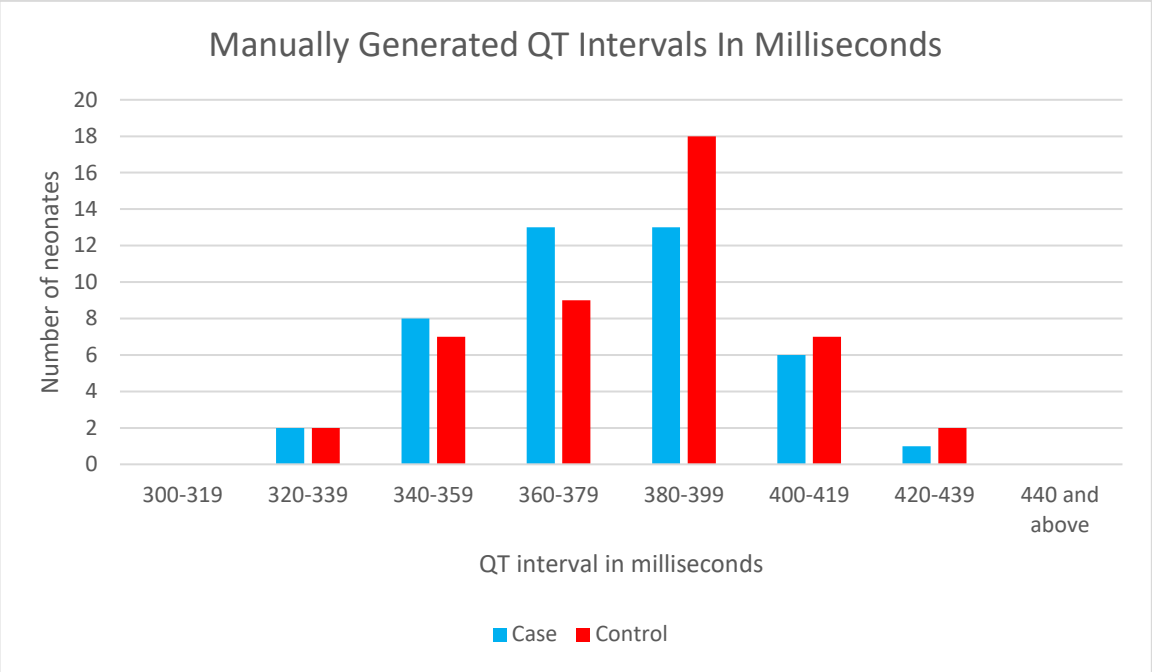
Figure 4. 9 Bar Chart Demonstrating the ECG Machine Generated Neonatal QT Intervals



4. 6. 4 Manually Generated Neonatal QT Intervals

The data generated manually by myself are utilised for the study analysis in this section, although the documented QT intervals from the Neonatal Consultant were similar. The mean manually generated QT intervals for the two groups were similar, being 376.4 milliseconds (SD= 22.95; 95%CI 369.5- 383.3) in the case group and 379.6 milliseconds (SD= 25.06; 95%CI 372.28- 386.88) in the control group. 72 (81.8 %) of all the study neonates had a manually generated QT interval of less than 400 milliseconds (figure 4.10). Unlike the machine generated QT intervals, where no QT intervals were >420 milliseconds, here one case group neonate had a QT interval of 433 milliseconds and two controls had QT intervals of 422 and 435 milliseconds respectively. However, there was no statistically significant difference between the two study groups regarding manually generated QT intervals (p= 0.534).

Figure 4. 10 Graph Demonstrating the Manually Generated Neonatal QT Intervals



Although the ECG machine generated QT interval and the manually confirmed QT intervals for both groups were similarly distributed and all less than 440 milliseconds, there was a statistically significant difference between the two methods (p= 0.019*) with the manually confirmed QT interval values being greater.

4. 6. 5 Inter-rater QT Intervals

The intra-rater recheck values for the QT interval were compared with original manually calculated QT intervals (figure 4. 10). The mean QT interval for the intra-rater recheck group was 377 milliseconds (SD= 25.31), was within normal parameters and only 3 milliseconds difference from the mean of the original manually generated QT intervals (380.15 (SD= 23.91). There is no significant difference between the 51 intra-rater QT interval group and the 51 original manually generated QT interval group (p=0.525), demonstrating the validity of the original manual assessment.

Results

There was a similar number of the intra-rater group that had a recheck QT interval value greater (n=25) or less than (n=23) than the original manually generated QT interval. Over half of the intra-rater QT interval values were within 10 milliseconds of the original value (n=32), although the maximum difference was -50 to +31 milliseconds. All intra-rater QT interval values were less than 440 milliseconds and there was no statistically significant difference between the case and control intra-rater groups when an independent sample t test was applied (p=0.384) (table 4. 14).

Table 4. 14 Intra-Rater Recheck Values of Manually Generated Neonatal QT Intervals

Intra-rater Recheck of Manually Generated QT Intervals	**Case**	**Control**	**All**
n (% of original sample)	27 (62.8)	24 (53.3)	51 (58)
mean (SD)	374.3 (27.23)	380.1 (19.64)	377.0 (23.91)
95% CI	364.3 to 384.3	372.23 to 388.03	370.44 to 383.64

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation

4. 6. 6 Covariate Analysis

In order to ensure the validity of the QT intervals achieved and justify the data collected to contextualise the findings, analysis of covariance was undertaken. As the ECG interpretation by machine has been shown to be as accurate as a

Cardiologist when the results are normal (Smulyan, 2018), as in this study, the ECG machine QT intervals were used for the covariate analysis. This statistical test generated ECG machine QT interval means, which then underwent linear regression evaluation against the variables of alcohol and smoking use in pregnancy, maternal medical history, maternal medicines (excluding SSRIs), and the gender & birth weight of the neonate. The results are detailed in table 4. 15.

Table 4. 15 Covariate Analysis of ECG Machine QT Interval Means With Alcohol and Smoking Use In Pregnancy, Maternal Medical History, Maternal Medicines (Excluding SSRIs), and the Gender & Birth Weight of the Neonate

Model	Unstandardized Coefficients- B	Unstandardized Coefficients- SD	p value~	95% CI
Constant	375.339	27.696	0.000	320.23 to 430.45
Smoking habits	6.821	4.576	0.140	-2.28 to 15.93
Alcohol in pregnancy	4.178	5.464	0.447	-6.69 to 15.05
Medications in pregnancy	1.574	0.926	0.093	-0.268 to 3.42
Birth weight of neonates	-3.024	6.192	0.627	-15.34 to 9.30
Gender of neonate	-6.966	5.785	0.232	-18.48 to 4.54
Maternal medical history	-1.202	1.137	0.293	-3.47 to 1.06

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation

Exposure to maternal smoking and alcohol in pregnancy increased the expected neonatal QT interval by 6.8 milliseconds (95% CI -2.28 to 15.93 milliseconds) and 4.2 milliseconds (95% CI -6.69 to 15.05) respectively when controlling for other potential confounders. Males had a QT interval 7 milliseconds (95% CI -18.58 to 4.5) shorter than female neonates when potential confounders were controlled for. In addition, lower birthweight (less than 3.372 kg) decreased the expected neonatal QT interval.

4. 6. 7 Summary of Neonatal QT intervals By All Methods of Assessment

As all the mean neonatal QT intervals were between 368.7 milliseconds and 380.2 milliseconds, they were all < 440 milliseconds and therefore within normal parameters. Bland Altman linear regression on the QT interval means of the three methods used to assess the QT intervals, demonstrated that for the most part all methods were a valid approach to utilise within this study. Although there was a significant difference between the ECG machine QT intervals and the original manual QT intervals (p=0.019*), there was no clinically important differences as a result of this. Further the validity of the original manual QT intervals were confirmed by the use of the intra-rater correlation tool and the non-significant p value from statistical comparison of the two groups (p=0.525).

4. 6. 8 Follow Up for Prolonged Neonatal QT Interval

No neonate in this study required follow up at six months of age to assess well-being after having a prolonged QT interval on the ECG performed at 48- 72 hours old.

4. 6. 9 Non- QT Interval ECG Anomalies Found in Neonates in Study

Six neonates, three case participants and three control participants, had borderline ECG anomalies that were not a prolonged QT interval. Four of these were male neonates, three of whom were cases and one a control, and the other two neonates were female and controls. Four had an axis that was on the higher end of normal and one had a non-specific anomaly in the T wave. A further poor-quality ECG warranted further investigation, but the neonate was subsequently found to be clinically well with no pathology. These women and their neonates were followed up as detailed below (table 4. 16). The electronic record system review at six months of age reported no pathology at six months of age for any of these six neonates.

Table 4. 16 ECG Anomalies Other Than Those Relating to the QT Interval

Gender	Study Group	Anomaly	Review of Electronic Record System At Six Months Old
Male	Case	Poor-quality ECG. QT interval normal. Repeat 3 weeks later with ECHO- Nil abnormalities seen. Repeat ECG at six weeks old- Nil abnormalities seen. Repeat ECG/ ECHO at four months old- Nil abnormalities seen.	Nil abnormalities seen
Male	Case	Superior axis. QT interval normal. Repeat ECG/ ECHO at eight days old- Nil abnormalities seen.	Nil abnormalities seen
Male	Case	Normal QT interval. Slightly broad T wave. -> Repeat- Nil abnormalities seen. Repeat at four weeks old- Nil abnormalities seen.	Nil abnormalities seen

Gender	Study Group	Anomaly	Review of Electronic Record System At Six Months Old
Male	Control	Borderline axis. Normal QT interval. One month old- Nil abnormalities seen. Two months old- Nil abnormalities seen. Four months old- Nil abnormalities seen. Five months old- Nil abnormalities seen.	Nil abnormalities seen
Female	Control	Poor quality ECG. QT interval normal.? superior axis. Negative p wave in lead two -> Repeat - Nil abnormalities seen	Nil abnormalities seen
Female	Control	Borderline axis. Normal QT interval. Two months old- Nil abnormalities seen. Three months old- Nil abnormalities seen.	Nil abnormalities seen

4. 7 Secondary Outcomes for the Study

The secondary outcomes for the study explored current SSRI treatment trends and maternal mental health, as detailed in the following sections. However, as this study only obtained 45% statistical power and the data analyses throughout this chapter were based on small sample size, there is potential for Type I and Type II error.

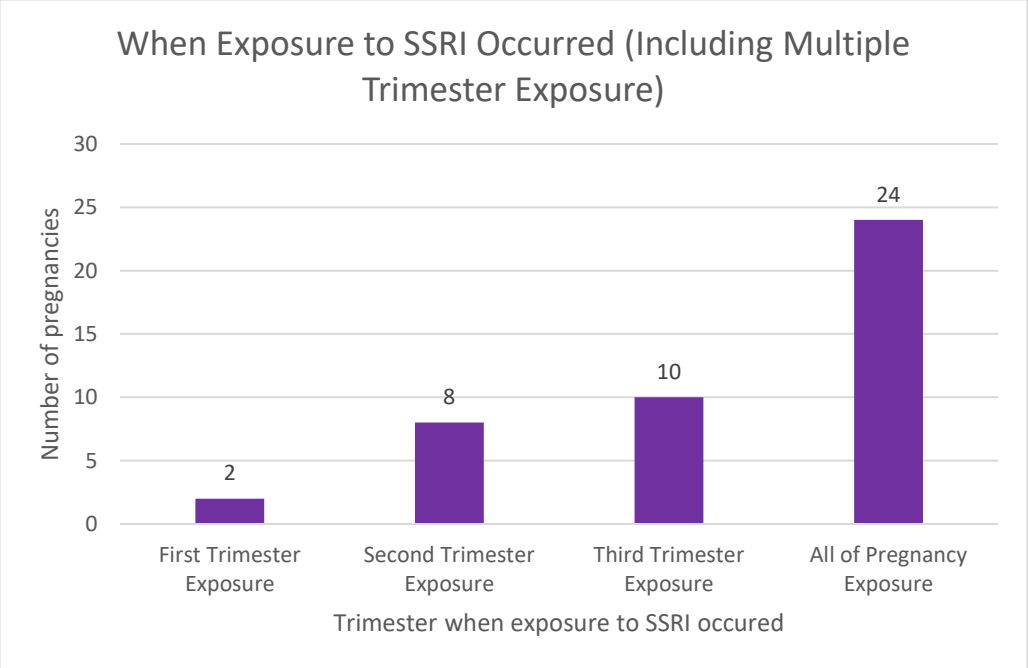
4. 7. 1 Data on SSRI Exposure in Pregnancy

Data were collected on the type of SSRI used by the cases, the dose of the SSRI used, and at what gestation the fetus was exposed to the medication. These data are detailed in the following section.

4. 7. 1. 1 When Did SSRI Exposure Occur

Of the women using SSRIs antenatally, 33 (77%) had started the medication pre-pregnancy, eight started the SSRI in the first trimester with the others starting their treatment in later pregnancy. Of the 33 women utilising SSRIs prior to pregnancy, 24 (73%) of them used them throughout the whole of their pregnancy and into the postnatal period (figure 4. 11). One woman discontinued citalopram to conceive, and three women on pre-pregnancy SSRIs, stopped taking the SSRIs in the first trimester. However, relapse of their mental health symptoms required all four women to restart treatment again at some point in their pregnancy and continue use after birth.

Figure 4. 11 Bar Chart Demonstrating Timing of Antenatal SSRI Exposure in Case Group Neonates



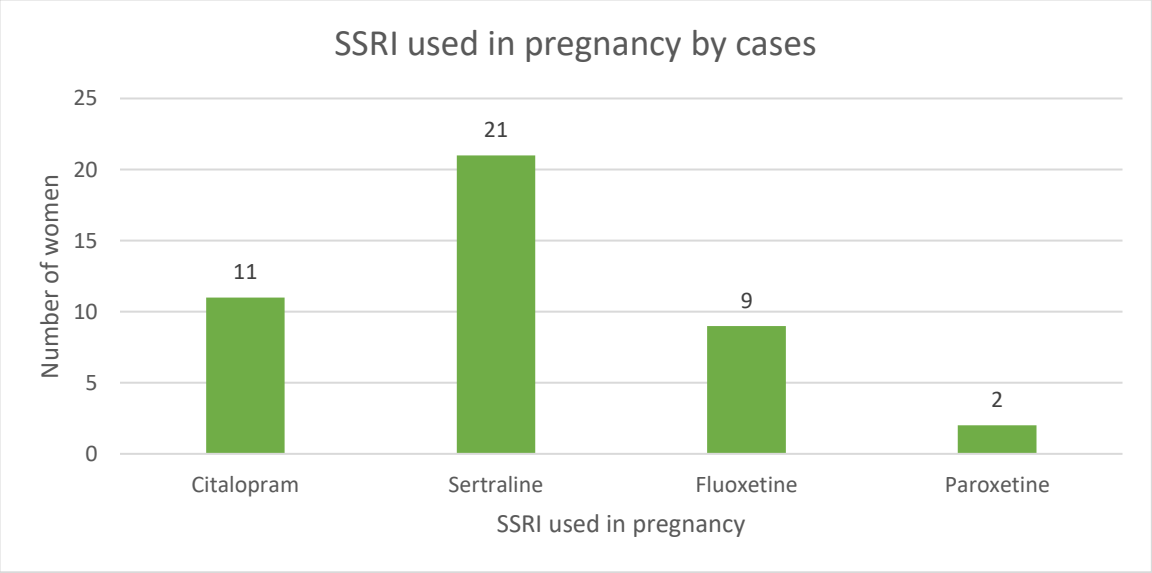
Ten women had the SSRI they were using changed to one with presumed lesser fetal effects when they wanted to conceive or when pregnancy was confirmed. This included changes from paroxetine, to citalopram and sertraline; from citalopram to sertraline; and from sertraline to paroxetine. Seven women required a therapeutic increase in the dose of the SSRI they

were taking antenatally. Three women took SSRIs until the third trimester, weeks 28, 30 and 32 respectively and did not restart use during the rest of their pregnancy.

4. 7. 1. 2 Type of SSRI Used by the Women in the Case Group

The main SSRIs utilised in pregnancy by the women in the case group are displayed below in figure 4.12. The commonest SSRI used antenatally was sertraline with 21 (49%) of the women in the case group ingesting it in pregnancy. Citalopram, fluoxetine and paroxetine were used by 11 (25%), nine (21%) and two (5%) of the women in the case group respectively.

Figure 4. 12 Bar Chart Demonstrating the Type of SSRIs Utilised by the Women in the Case Group



4. 7. 1. 3 Doses of SSRI Used by the Women in the Case Group

All doses of SSRI used by the women in the study were within the recommended dose for that particular medication, although some women used doses of

sertraline and citalopram that were on the higher limit of that recommendation (table 4. 17).

Table 4. 17 Doses of SSRI Used by the Women in the Study

Medication	Dose Range (mgs/day)	Recommended Dose
Sertraline	20- 200	Up to 200mgs/ day (drugs.com, 2012f)
Fluoxetine	20- 60	Up to 80 mgs/ day (drugs.com, 2012c)
Citalopram	10- 40	Up to 40 mgs/ day (drugs.com, 2012a)
Paroxetine	20	Up to 60 mgs/ day (drugs.com, 2012e)

Further analysis was undertaken to assess whether there was any significant difference between the neonatal QT intervals of those who were exposed to citalopram in pregnancy and those exposed to other types of SSRIs (table 4. 18).

Table 4. 18 Statistical Analysis of ECG Machine Generated Neonatal QT Intervals When Those Exposed to Citalopram Antenatally Were Assessed Against Those Exposed to Other SSRIS

p Value~ of Neonatal QT Intervals When Compared For Antenatal Exposure To:	Fluoxetine (n=9)	Sertraline (n=21)	Paroxetine (n=2)	All SSRIs (n= 32)
Citalopram (n=11)	0.109	0.402	<0.001*	0.375

~significance level =0.05

There was no statistically significant difference between the ECG machine generated neonatal QT intervals when they were assessed using an independent sample t test for antenatal exposure to citalopram compared to fluoxetine (p=0.109) or sertraline (p=0.402). However, there was a significant difference when the ECG machine generated QT interval for antenatal exposure to citalopram was assessed against that of paroxetine (p= <0.001*).

4. 7. 2 Maternal Mental Health History

All but one woman in the case group had reported a mental health history of depression or anxiety/ stress disorders (table 4. 19). Anxiety was reported as including panic attacks, stress as a result of the working environment and being triggered by a family death. One control reported having depression in the past but was no longer affected or receiving treatment for it (table 4. 19). Crosstabulation of these data are presented in the table below.

Table 4. 19 Crosstabulation of Reported Mental Health History for Women in Study

Maternal Mental Health History, n (%)	Case	Expected Count^	Control	Expected Count ^	All	Expected Count ^
Depression	24 (55.8)	12.2	1 (2.2)	12.8	25 (28.4)	25
Anxiety/ Stress	18 (41.9)	8.5	0 (0)	9.2	18 (20.5)	18
Eating disorders	1 (2.3)	0.5	0 (0)	0.5	1 (1.1)	1
Overdose	0 (0)	21.5	0 (0)	22.5	0 (0)	44
Total	43 (100)	43	1 (2.2)	45	44 (50)	88

^ Crosstabulation ~significance level =0.05

The following sections discuss other data collected during the data collection sheet completion. Firstly, pregnancy outcomes for women in the study are reported (section 4. 8) followed by the outcomes for their neonates (section 4. 9; table 4. 12).

4. 8 Pregnancy Outcomes for Women in the Study

Data were collected on the pregnancy outcomes for the women in both study groups and these focused on antenatal ultrasound outcomes and mode of delivery. The data are summarised in table 4.20 and detailed in the following section with consideration to the primary outcome, the neonatal QT interval, where appropriate.

Table 4. 20 Summarisation of Data Relating to Pregnancy Outcomes for Women in the Study

Pregnancy Outcome	Case	Control	Total	Pearson's Chi Square Test p value
Antenatal Ultrasound Outcomes n=				
Nil of note	27 (62.8%)	36 (80%)	63 (71.6%)	
Concerns (fetal/placental)	16 (37.2%)	9 (20%)	25 (28.4%)	
Mode of delivery n=				
Normal vaginal	23 (53.5%)	17 (20.5%)	40 (45.5%)	
Instrumental	3 (7%)	13 (28.9%)	16 (18.2%)	
Caesarean section	17 (39.5%)	15 (33.3%)	32 (36.3%)	
				0.03*

~significance level =0.05 n= number

4. 8. 1 Antenatal Ultrasound Outcomes

27 (62.8%) of the women in the case group and 36 (80%) of the women in the control group had no concerns noted on antenatal ultrasound (table 4. 20). 14 of the women in the case group and nine of the women in the control group had fetal issues. These included poor growth in the fetus, large for gestational size, small for gestational size, breech position of the fetus, syndromic potential and polyhydramnios. One woman in the case group was noted to have placenta praevia and another an anterior placenta. Crosstabulation demonstrates that the women in the case group were less likely to have normal antenatal ultrasound outcomes than expected and that those in the control group were more likely. Concerns regarding the fetus were greater than expected for the women in the case group, but less than expected for those in

the control group. This difference is not clinically important in regard to this study and the reasons why this may have occurred are discussed further in section 5. 4. 1.

4. 8. 2 Mode of Delivery of Study Participants

23 (53.5 %) of the women in the case group birthed by normal vaginal delivery compared to 17 (37.8%) of those in the control group (table 4. 20). 20 of case group women received intervention strategies at birth, with the majority of these being by Caesarean section and the rest by instrumental methods (forceps or ventouse delivery) (table 4. 20). Within the control group, a similar number of women required intervention strategies by instrumental methods (n=13) and by Caesarean section (n=15). There was a statistically significant difference between the two study groups regarding mode of delivery (p=0.03) but here there is potential for type I error (table 4. 20).

When the effect of delivery mode on QT interval was analysed with an independent sample t test, there was no statistically significant difference noted between any birthing methods (table 4. 21). The potential rationale for the delivery mode pattern noted in this study is discussed in section 5. 4. 1.

Table 4. 21 Analysis of Neonatal ECG Machine Generated QT Interval When Assessed Against Mode of Delivery

p Value~ of Neonatal ECG Machine Generated QT Interval When Assessed Against: -	Normal Vaginal Birth
Instrumental Method	0.81
Caesarean Section	0.12

~significance level =0.05

The significant difference regarding the timing of the ECG noted in section 4. 6. 1 between the study groups, was not influenced by the mode of delivery. When

assessed against the mean age of the neonates (55 hours old) at the time of ECG procedure, there was no statistically significant difference as to whether the ECG was done before or after the age of 55 hours old (p=0.17) in relation to mode of delivery (table 4. 22).

Table 4. 22 Analysis of Mode of Delivery Assessed Against Timing of ECG

Method of Birth (n)	Less Than 55 Hours Old at Time of Delivery	More Than 55 Hours Old at Time of Delivery	Totals	Pearson's Chi Square Test p Value~
Normal Vaginal Delivery	24	15	39	
Instrumental Delivery	6	11	17	
Caesarean Section	19	13	32	
Totals	49	39	88	0.17

~significance level =0.05

4. 9 Neonatal Demographics

The following section presents the neonatal demographic data for both study groups that were documented on the data collection sheet for the study and summarised in table 4.12. These data are considered in association with the primary and secondary outcomes where appropriate.

4. 9. 1 Gestation at Birth of Neonates Recruited to the Study

50 (57%) of all the neonates in the study were born before their estimated date of delivery, with a mean gestational age of 39 weeks and 4 days (table 4. 12, table 4. 23). There was no statistically significant differences between the study groups in relation to gestation at birth (p=0.14) (table 4. 12).

Table 4. 23 Gestation at Birth of Neonates Recruited to the Study

Gestation at Birth (weeks)	Case	Control	All
37-39, n (%)	27 (62.8)	23 (51.1)	50 (56.8)
40 and over, n (%)	16 (37.2)	22 (48.9)	38 (43.2)
Total	43 (100)	45 (100)	88 (100)

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation

Additionally, when the ECG machine generated QT interval for those neonates born before 40 weeks gestation was compared to the ECG machine generated QT interval for those born 40 weeks gestation and above using an independent sample t test, there was no significant difference noted (p= 0.137).

4. 9. 2 Gender of Neonates Recruited to the Study

Whilst the majority of neonates in the case group were male (n=25 (58.1%)) and the majority of the neonates in the control group were female (n=23 (51.1%)), there was no statistically significant difference between the groups (p=0.40) (table 4. 12). There was also no statistically significant difference between the gender of the case group neonates and maternal mental health issues (p=0.521) (table 4. 24).

Table 4. 24 Analysis of Maternal Mental Health Concerns in Regard to Gender of Neonate

Group	No Maternal Mental Health Concerns	Maternal Mental Health Concerns	Totals	Pearson's Chi Square Test p Value~
Male	22	25	44	
Female	22	19	44	
				0.521

~significance level =0.05

4. 9. 3 Birth Weight of Neonates Who Had an ECG

The birth weight of the neonates ranged from 2310 grams to 4580 grams (table 4. 25). The smallest case group neonate was 140 grams smaller than the smallest neonate in the control group (table 4. 25). The largest birthweight however was similar in both the case and control group neonates (table 4. 25). The mean weight was 3372 grams and there was a statistically significant difference between the birthweights of the case and controls (p=<0.001*) (table 4. 12).

Table 4. 25 Birthweight of Neonates Recruited to the Study

Birth Weight of Neonate (grams)	Case	Control	All
2000- 2500, n	2 (4.7)	1 (2.2)	3 (3.4)
2501- 3000, n	9 (20.9)	9 (20)	18 (20.5)
3001-3500, n	17 (39.5)	19 (42.2)	36 (40.9)
3501-4000, n	10 (23.3)	11 (24.5)	21 (23.9)
4001-4500, n	5 (11.6)	4 (8.9)	9 (10.2)

Birth Weight of Neonate (grams)	Case	Control	All
4501-5000, n	0 (0)	1 (2.2)	1 (1.1)
Total, n	43 (100)	45 (100)	88 (100)
Minimum	2270	2410	2310
Maximum	4500	4580	4580
Median	3220	3360	3350

~significance level =0.05 CI= Confidence Interval SD=Standard Deviation

4. 9. 4 Postnatal Course for Neonates Recruited to the Study

4. 9. 4. 1 Neonatal Problems of Study Participants

Most neonates had no postnatal problems, with 25 (58.1%) of cases and 36 (80%) of controls being fit and well from birth until the point of recruitment, despite treatment for suspected sepsis in the latter (table 4. 12). However, there were fewer fit and well case group neonates than expected, and conversely more control group neonates than expected that were. Eight (18.6%) of the cases were found to be jittery versus none of the controls. Five (11.6%) case and seven (15.6%) controls had feeding problems that required intervention such as breastfeeding support and active feeding management).

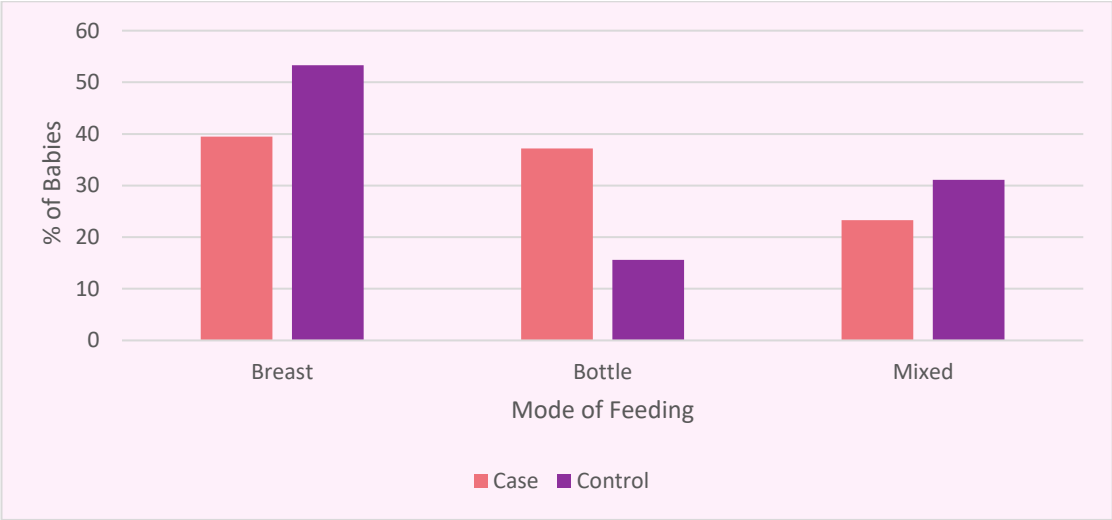
4. 9. 4. 2 Neonatal Examination of Study Participants

65 (74%) of study neonates had normal newborn examinations (table 4. 12) and matched the expected count for this parameter in crosstabulation. Six (14%) case group neonates had positional talipes versus three (6.7%) control group neonates.

4. 9. 4. 3 Mode of Feeding

17 (39.5%) of cases breastfed with the remainder either artificial (n=16) or mixed feeding (n=10) (figure 4. 13; table 4. 12). Over half of the controls were breastfed (n=24) (figure 4. 13; table 4. 12). There was no significant differences between the groups in regard to all forms of feeding (p=0.69), nor was there with regards to breast and mixed feeding (p=0.682) (mean difference= -0.23, 95% CI -1.34 to 0.88), however there was between breast and artificial feeding (p=0.03*) (mean difference= 0.28, 95% CI 0.03 to 0.54). The reasons for a difference between the two groups in regard to feeding preference and choice are discussed in section 5. 4. 2.

Figure 4. 13 Bar Chart Demonstrating the Mode of Feeding Per Study Group



Assessment of the impact from breastmilk transfer of SSRIs to the neonate is quantified by the ingestion of more or less than 10% of the maternal serum concentration (Pinheiro et al, 2016). When those neonates who received any breastmilk were compared with regard to whether their antenatal exposure was to a SSRI that had a higher or lower maternal dose transfer rate (n=27; 63%) versus those who received no breastmilk (n=16; 37%), there was no significant difference (p= 0.324) (table 4. 26). It can also be seen that more neonates received breastmilk (n=16; 59%)) when the antenatal exposure was to an SSRI with a lower

transfer rate of the maternal dose in the milk rather than higher (n=11; 41%) (table 4. 26).

Table 4. 26 Ingestion of Any Breastmilk Versus None When the Transfer Rate in Breastmilk of the SSRI Used Antenatally Was Considered

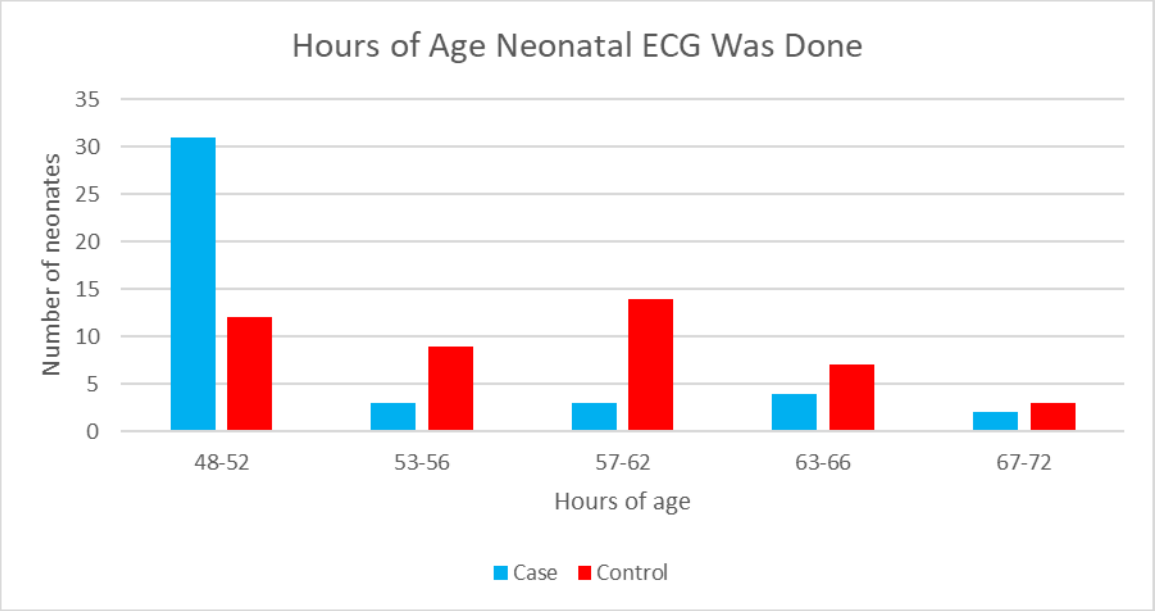
Feeding n (%)	Neonates with Antenatal Exposure to SSRIs with Lower Transfer of Maternal Dose in Breastmilk (Sertraline/ Paroxetine)	Neonates with Antenatal Exposure to SSRIs with Higher Transfer of Maternal Dose in Breastmilk (Citalopram/ Fluoxetine)	Totals	Pearson's Chi Square Test p Value~
Any Ingested Breastmilk	16	11	27	
No Ingested Breastmilk	7	9	16	
Totals	23	20	43	0.324

~significance level =0.05

4. 9. 5 Age in Hours at Which the ECG Was Performed

The mean age that neonates in the case group underwent the ECG was 52 hours and eight minutes (SD= 6.44; 95% CI 50.16 to 54.12). However, the mean age at which the controls had the ECG was 57 hours and 28 minutes (SD= 6.00; 95% CI 55.66 to 59.27). This difference means the case group neonates underwent an ECG, on average, 5 hours and 20 minutes earlier than for the controls. This mean age difference between the two study groups was statistically significant (p=<0.0001*). 31 (72%) of case group neonates received their ECG at 52 hours old or less The largest proportion of neonates in the control group (n=14 (31.1%)) had their ECG between 57 and 62 hours old (figure 4. 14).

Figure 4. 14 Bar Chart Demonstrating the Age in Hours at Which the Neonatal ECG was Performed



4. 10 Summary

This study was undertaken to ascertain whether there was an association between antenatal SSRI exposure and a prolonged neonatal QT interval on an ECG performed at 48- 72 hours of age. The chapter has demonstrated that this study has found no such association between this medication and the neonatal QT interval. However, this study only obtained 45% statistical power and the data analyses throughout this chapter were based on small sample size with the potential for Type I and Type II errors when the data are subjected to statistical analysis.

This chapter detailed the results of the study, including the screening process, the data gathered on the 88 women and neonates recruited to the study, and the similarities & differences between the case and control groups, using statistical analysis. The statistically significant differences and non-significant differences

between the case and control women and neonates are summarised in table 4. 27 and 4. 28 below.

Table 4. 27 Statistically Significant Differences Between the Case and Control Groups

Aspect	p Value
Age in Hours at Which the ECG Was Performed	<0.0001
ECG Machine v Manually Generated QT Interval	0.019
Maternal Ethnicity	0.004
Maternal Smoking Behaviour	0.015
Maternal Antenatal SSRI Use	0.00
Maternal Mental Health History	0.00
Mode of Delivery	0.03
Birthweight of Neonate	<0.001

Table 4. 28 Non-Statistically Significant Difference Noted Between the Case and Control Groups

Aspect	p Value
QT interval >440 milliseconds	1.00
ECG machine generated QT interval	0.943
Manually generated QT interval	0.534
Intra-rater recheck of manually generated QT interval	0.384
Intra-rater recheck v original manually generated QT interval	0.525
Normal vaginal delivery v instrumental delivery in regard to QT interval	0.81
Normal vaginal delivery v Caesarean section in regard to QT interval	0.12
Alcohol use	0.152
Mode of delivery v age at ECG	0.17
Gestation at birth	0.14
Gender of neonate v mental health problems	0.52
Mode of feeding	0.69

SSRI usage in the case group demonstrated that sertraline was used most commonly antenatally (49%), and that most of the women in the study took the SSRI throughout their pregnancy (73%). Most women were on SSRIs for reported

depression (55.8%) or anxiety/ stress (41.9%). ECG abnormalities that occurred were also reported and the wellbeing of the all six affected neonates confirmed at six months of age.

The following chapter discusses the results achieved for the primary and secondary outcomes, two interesting findings of note and the strengths and weakness of the study method and methodology. This is in the context of national and world-wide initiatives in mental health management, quality improvement and research.

5 Discussion

5. 1 Study Summary

It is important that neonatal care is based on robust evidence-based knowledge. This principle underpins my role as an ANNP, which includes the provision of postnatal care guidance for neonates exposed to SSRIs antenatally. Evidence regarding SSRI use in pregnancy had previously found an association with congenital abnormalities such as structural cardiac defects (Berard et al, 2015), PPHN (Reis et al, 2010), prematurity (Huang et al, 2014) and NAS (Levinson-Castiel et al, 2006) but limited data were available that related specifically to the effects of antenatal exposure on the electrical cardiac system of the neonate, specifically the QT interval (Degiacomo et al, 2016; Dubnov et al, 2005; Dubnov-Raz et al, 2008). This lack of data shaped the null hypothesis and this study was designed to research this within the context of clinical practice and doctoral study.

A case -controlled study was developed that sought to compare the effects of antenatal SSRI exposure on the neonatal QT interval versus no exposure. The cases were compared with a proxy, low risk group of neonates whose mothers hadn't taken SSRIs in pregnancy and were healthy, but remained in hospital at 48- 72 hours as there was a theoretical risk of sepsis. Despite its limitations (section 2. 2. 1), a pragmatic approach to calculate sample size was taken, and utilised the findings of the only other published case-controlled study looking at this effect on the neonatal QT interval (Dubnov-Raz et al, 2008). These findings calculated a sample size of 121 neonates per group. Data collection for the study was undertaken over an 18- month period in 2016-2017 during which 43 case and 45 control group neonates had an ECG. Due to sample size, a statistical power of 45% was achieved. Recruitment was hindered by clinical workload, a lack of awareness of factors such as extended antibiotic use & other antidepressant use in pregnancy, and a small research team with a clinical commitment.

The neonates in both study groups had a normal QT interval, with the case group receiving their ECG five hours earlier than the control group neonates (section 4. 9. 5, page 139). However, this finding was unlikely to be clinically significant with regard to the neonatal QT interval and occurred due to the preference of the case group women to leave hospital as soon as the period of neonatal observation for SSRI exposure was completed. The later timing of the control group neonatal ECG was due to the requirement to wait for blood culture results and subsequent assessment of the neonate by the ANNP / Clinical Fellow, as clinically well. As all ECGs occurred after the timeframe for increased QT interval variability (Schwartz et al, 1982) and between 48- 72 hours, there is no theoretical reason to suggest that the age difference between the groups due to process, impacted on the resulting QT interval.

Follow up data was collected between August 2017 – February 2018, on six neonates who had non- QT interval, electrical abnormalities noted on initial ECG, but all were assessed via the EPR system as having no episodes of hospital review or admission to the hospital before six months of age, and were therefore considered fit and well (section 4. 6. 9, page 125-126). These isolated ECG anomalies were probably due to latent neonatal transition postnatally, but poor ECG technique was implicated in one episode.

Most of the women in the case group had a medically documented history of depression and anxiety (n=42; 99.7%) (section 4.7.2, page 130). Sertraline was the most commonly used SSRI in pregnancy (n= 21; 49%), followed by citalopram (n=11; 25%). All doses of SSRIs ingested were within the recommended doses for those medications (section 4. 7. 1, page 126).

The case group mothers were on average older than those in the control group (32.4 v 30.6 years) (section 4. 5. 1, page 104). This is consistent with reported demographics from the Levison-Castiel et al (2006) study where SSRI exposed women had a mean age of 32.8 years (+/- 5.3) and the control group women had a

mean age of 30.7 years (+/- 5.7). Although under 18-year-old women were excluded from this study due to ethical considerations, these results were similar to the total birthing cohort, where within the same timeframe, the youngest woman to birth at the DGH was 17 years of age and the oldest was 53 years old. Within the study timeframe, the mean age amongst the total birthing cohort at the DGH was 30.5 years, which was similar to the national mean of 30.4 years old in 2016 (Office of National Statistics, 2016). The slightly greater mean age of women in the study may have been an artefact of the age inclusion criteria for the study set by the Research Ethics Committee.

The case group women were more likely to be of white British origin (n= 41 (95.3%) v n=32 (71.1%)), and smokers (n=13 (30%) v n= 4 (9%)) who drank alcohol in pregnancy (n=6 (14%) v n=2 (4%) (section 4. 5. 3, page 105-107). Consistent with published research (Norby et al, 2016), a greater proportion of women who had smoked in pregnancy at any time were in the case group, however, this could be interpreted as a coping strategy when dealing with mental health problems or a product of lifestyle/ background. As smoking affects placental vasculature, these results could potentially impact on other collected data with regard to birthweight and postnatal outcomes. The Saving Babies Lives care bundle (NHS UK, 2019c) seeks to reduce smoking in pregnancy, and could therefore improve the impact of antenatal smoking on the neonates. A reduction in antenatal smoking could also reduce the need for pregnancy surveillance and ultrasound screening, with its associated potential increase in interruption of pregnancy by instrumental or surgical delivery. Here, however, maternal smoking in pregnancy itself is unlikely to affect the QT interval of exposed neonates, as it is not associated with a prolonged QT interval in adults (Zhang et al, 2011), but it cannot be excluded due to physiological differences. There is no theoretical reason to suggest that these aspects would impact on the neonatal QT interval and are probably as a consequence of type I and type II error.

No women in either study group took recreational drugs in pregnancy. In contrast to the case group women, the largest proportion of the control group

women were fit and well (n=16, 36%). Maternal diabetes and hypothyroidism did not seemingly impact on the study results, although this may be as a result of type 2 error. No women with epilepsy was included in the study.

The case group women were more likely to give birth normally before term, to male infants who were on average 80 grams lighter than their counterparts. The control group women were more likely to deliver female infants, but were equally likely to give birth by all methods of delivery, and delivery was as likely to occur before as after their estimated date of delivery. The case group neonates were equally likely to be breast or artificially fed. Both the case (n=17; 39.5%) and control (n=15; 33.3%) groups had unexpectedly high rates of delivery by Caesarean section which was probably due to study methodology.

The case group neonates were more likely to be jittery (n= 8; 18.6%) (section 4. 9. 4. 1, page 137). Jitteriness can be a sign of hypoglycaemia (Holton, 2015), electrolyte imbalance (Widimsky, 2008) possibly because of poor feeding, infection, seizures and drug exposure not only from SSRIs but also nicotine. It has already been established in section 4. 5. 3. 1 that those recruited to the study with mental health problems were more likely to smoke, so potential jitteriness from SSRI or nicotine exposure is not unexpected. The ANNP / Clinical Fellow would have undertaken a clinical assessment of the neonate for likely pathology and treated accordingly. The brief nature of the jitteriness did not prevent those neonates from being included in the study if it was no longer evident at recruitment, and the neonates were clinically well.

SSRI exposure in pregnancy has been found to increase the incidence of positional talipes (Colvin et al, 2011), and in this study double the number of cases (n=6) versus the controls had positional talipes (section 4. 9. 4. 2, page 137). However, with such small numbers having positional talipes, this is likely to be due to type I error.

Covariate analysis of the neonatal QT intervals in regard to the effects of maternal smoking, antenatal maternal alcohol use, maternal medical history, maternal medication, as well as the gender and birthweight of the neonate, found only a minimal effect on the QT interval of a maximum of 15 milliseconds across the individual factors.

Whilst the study was underpowered, it has a comparable sample size to the only other case-controlled study (Dubnov-Raz et al, 2008) investigating the neonatal QT interval in this context. It has been conducted prospectively with more rigor with respect to the timing of the ECG and the gestation at which the ECG was done, but did not find any neonates in either group with a prolonged QT interval (>440 msecs). It has also provided data on the secondary outcomes regarding maternal mental health concerns and SSRI use, and noted some interesting findings with regard to mode of delivery and feeding outcomes, all of which will be discussed in the following sections along with the limitations and strengths of the study method used.

5. 2 Primary Outcome

5. 2. 1 Prolongation of the Neonatal QT interval (>440 msecs)

This case-controlled observational study was designed to ascertain whether there was an association between antenatal exposure to SSRIs and a prolonged QT interval (>440 msecs) in a term neonate at 48-72 hours of age, or not. No prolonged QT intervals were noted for any of the neonates in the study regardless of exposure (section 4. 6). This absence of ECG pathology could have been due to there being no association between antenatal exposure to SSRIs and QT interval abnormalities, or because of potential type I or type II error.

The absence of prolonged QT intervals for the case group neonates in this study was not consistent with the findings of the Dubnov-Raz et al (2008) study. Here,

none of the 43 neonates exposed to antenatal SSRI had a prolonged QT interval (>440msecs) versus six of the 52 case group neonates in the Dubnov-Raz et al (2008) study. Reported data from the five neonates with QT intervals >460 msecs demonstrated three of the neonates had been exposed to paroxetine and two to fluoxetine (Dubnov-Raz et al, 2008). With the paroxetine prescribing changes as a result of the FDA (2006) reclassification (Charlton et al, 2015), similar studies which include large numbers of paroxetine exposed neonates are unlikely to occur. This study's results in regard to fluoxetine are not comparable either. The contrasting results despite similar sample size in both studies would suggest that the Dubnov-Raz et al (2008) study is potentially similarly underpowered and indicating possible type I and type II error. This finding was discussed with the University Statistician. He calculated that no SSRI exposed neonates having a prolonged QT interval in this study versus the 12% (>440 msecs) reported in the Dubnov-Raz et al (2008) study would only have happened 0.4% of the time, and it therefore suggests that a much larger sample size in the order of tens of 1000s would probably have been required and this would not have been clinically feasible.

The comparison of this study's findings with the Dubnov-Raz et al (2008) study suggests that the incidence of a prolonged QT in the antenatally SSRI exposed neonate is less common than previously thought.

This study addressed potential causes of Type I error in the Dubnov-Raz et al (2008) study with a more valid prospective study design and methodology. This included the gestation of the study participants, the postnatal age at which the ECGs were performed and the process for acquisition of information from the mothers of the neonates recruited to the study (section 3. 2. 3). These differences in study design could account for some of the disparity seen between the two studies. Type II error could also have occurred due to small sample size in the Dubnov-Raz et al (2008) study.

In the Dubnov-Raz et al (2008) study, four of the five neonates with a prolonged QT interval >460msecs had an ECG performed between 3- 30 hours old, which as it is considered the neonatal QT interval transition period, may have impacted the result especially as one was preterm. A study of 44, 269 QT interval readings in the newborn (Ulrich et al, 2014), confirmed earlier data that the QT interval is variable in the first few days of life for term neonates (Schwartz et al,1982), but also found that it was even more so for preterm neonates. Term neonates were found to have QT intervals of 444 msecs +/- 37 on day one and 429 msecs +/- 25 on day two, with preterm neonates having values of 452 msecs +/- 39 and 452 msecs +/- 34 on day one and two respectively (Ulrich et al, 2014).

The longest QT interval from the Dubnov-Raz et al (2008) study was 543 msecs in a 30-hour old, term neonate, which then normalised by the time of the repeat ECG the next day (Dubnov-Raz et al, 2008). In addition, the prolonged QT interval in a 3-hour old neonate had normalised two days later. If the timing of the ECGs in the Dubnov-Raz et al (2008) had been in accordance with this study, then these two neonates may have had a QT interval within normal parameters (section 3. 2. 3).

Case notes were used to retrospectively acquire important information on the mothers of the participants in the Dubnov-Raz et al (2008) study, yet these can be unreliable and prone to measurement error if incorrect or incomplete, and there was no cross- checking with the women themselves regarding SSRI use in pregnancy. For this study, women confirmed the data taken from case notes including SSRI used, when the data collection sheet was completed (section 3. 2. 6. 1), thus improving the validity of the findings and the strength of the study.

The data collected from the Dubnov-Raz et al (2008) occurred between 2000 and 2005. Three of the women in their study used 20 milligrams of paroxetine a day and the other two women used 30- 60 milligrams fluoxetine. These dosages are within normal recommended doses for these SSRIs (drugs.com, 2012c; drugs.com, 2012e; table 4. 17). Since the Dubnov-Raz et al (2008) study's period

of data collection, there has been an increased awareness of dose dependent effects from SSRI exposure that has precipitated dose restriction measures (Medicines and Healthcare Products Regulatory Agency UK, 2011; Vieweg et al, 2012 and reclassification of the use of paroxetine in pregnancy (FDA, 2006). Mental health care pathways also now recommend using the lowest dose with efficacy (*[local area] NHS UK, 2016). These restrictions may have meant that specifically the type and potentially the dose of SSRI utilised by the women in this study did not met the threshold for effect on the neonatal QT interval and therefore led to the difference seen between the studies' results.

The demographic data collected from the women and neonates in this study contextualised the QT interval values, provided the opportunity to ascertain any unknown associations between the antenatally SSRI exposed and unexposed neonate, and allowed covariate analysis of factors that may potentially have impacted the QT interval. Indeed the covariate analysis demonstrated that the antenatal maternal smoking and alcohol use, female neonatal gender and higher birthweight, could each in themselves minimally increase the expected QT intervals (section 4. 6. 6). Although, all of these neonates had QT intervals within normal parameters, further research could usefully specifically examine the effect of antenatal exposure to SSRIs in relation to these variables. The Dubnov-Raz et al (2008) study did not report such analysis or context for its data, thus again improving the validity of the findings and the strength of this study.

So, with the lack of neonates exposed to antenatal paroxetine, the higher gestational age of the included neonates, the consistently later postnatal age at which the ECGs were performed, and the more robust process for gaining information and cross-checking SSRI use the mothers, this prospective study would seem to provide a more valid answer to the research question despite its limited power and method.

Two further published, single subject case studies found a prolonged QT interval in response to antenatal exposure to fluoxetine (Dubnov et al, 2005) and the newer escitalopram (Degiacomo et al, 2016). In the first case study, the neonate had a routine ECG at 30 hours of age and had a QT interval of 540-580 msecs (Dubnov et al, 2005). This normalised to 380 and then 360 msecs over the following days. This neonate may have had a normal QT interval, if the ECG had been done within appropriate physiological parameters, reflecting a potential bias that this study excluded (section 3. 2. 3). In the second case study, the neonate was noted to have a prolonged QT interval when they were admitted to the neonatal unit in poor condition with serotonin toxicity at 9 hours of age. The QT interval was 531 msecs at that time, and was still prolonged on day 5, but normal by day 10 (Degiacomo et al, 2016). Whilst my study did not recruit any neonates with antenatal exposure to escitalopram (section 4. 7. 1. 2), it did however recruit 11 cases who were antenatally exposed to the similar SSRI, citalopram, and no prolonged QT intervals were identified (section 4. 7.1. 2).

The normal parameters for the QT interval used in all three studies (Degiacomo et al, 2016; Dubnov et al, 2005; Dubnov-Raz et, 2008) is two or three standard deviations from the mean when QT interval stability is achieved, so statistically 2.28% to 0.14% of neonates will have a QT interval greater than these parameters after 48 hours of age with no pathology. Some of the reported data in the studies may have reflected a normal clinical presentation despite being outside of normal statistical parameters at the time the ECG was taken. Despite this statistical assumption, this study identified no neonatal prolonged QT intervals, so there is risk of type II error.

These studies (Dubnov et al, 2005; Degiacomo et al, 2016) confirm that single case reports are a potentially useful tool for highlighting concerns, but larger studies with appropriate methodology are required to verify effects (Koren et al, 2012). Although this case-controlled study was underpowered and with the potential for type II error from small sample size, it provides data with greater

validity when compared to the main body of evidence to date, and reassuringly did not find any abnormal QT intervals in this population.

5. 2. 2 Prolongation of the Neonatal QT Interval Within Normal Parameters in Response to Antenatal Exposure to SSRIs

Although not addressed in these three studies (Degiacomo et al, 2016; Dubnov et al, 2005; Dubnov-Raz et, 2008), some data (Sorlini et al, 2013) have also suggested that antenatal exposure to citalopram specifically, may prolong the neonatal QT interval without causing it to extend outside of normal parameters. Sorlini et al (2013) posted a comment response to a study which detailed prolongation of the QT interval from citalopram exposure in adults (Castro et al, 2013), and reported its effect on the QT interval in antenatally exposed neonates: - 19 neonates exposed to antidepressants or antipsychotic drugs were compared to 14 undefined controls. The neonates with antenatal exposure to citalopram (n= 4) were reported to have a significantly longer QT interval than either the controls (414+30 msecs vs 380+17msecs; p=0.0008) or those exposed to other antidepressant or antipsychotic medications (414+30 msecs vs 375+17 msecs; p=0.04) on day three, and at one month of age. Very small sample size (n=4) in the Sorlini et al (2013) comment may have increased the potential for type I error compared to my larger study (section 4. 5). My study found no significant difference between the QT interval values for citalopram (n=11) v all other SSRIs (n=32) in the study (p= 0.375), but again this study is underpowered for such an analysis and at risk of type II error. The data in the Sorlini et al (2013) comment included six neonates with antenatal exposure to paroxetine, escitalopram and fluoxetine, and in contrast to the three studies discussed in section 5. 3 .1, no prolonged QT intervals were reported. As the data have not been formally published outside of the Sorlini et al (2013) comment, it is difficult to assess the rigour of the reported data.

It is clear that all studies discussed in this section present with methodological deficits that may have produced type I error. This prospective study answers the research question with greater rigor, by virtue of sample size and timing of ECGs, despite the potential for type II error. The next section considers the secondary outcomes for this study, namely the type of SSRI used in pregnancy and maternal mental health disorders.

5. 3 Secondary Outcomes

5. 3. 1 Type of SSRI Used in Pregnancy

Of the case group women in this study, 21 (49%) used sertraline in pregnancy, 11 (25%) used citalopram, nine (21%) used fluoxetine and paroxetine were used by the other two (5%) women. The type of SSRI that was utilised in pregnancy was self-reported and checked with the woman during the data collection process. In addition, the dose of SSRI taken, during which trimester(s) the SSRI was ingested and any changes to pharmacological management such as adjustment of dose or change to SSRI type were also noted. Pregnancy induced physiological changes which can affect absorption and metabolism may have required some women to increase the SSRI dose, as well as external factors affecting their mental health.

Whilst in the past, national guidance supported the use of fluoxetine as a treatment option for pregnant women, neither the updated integrated perinatal mental health pathway used by the DGH (*[Local area] NHS UK, 2016) nor the updated national guidance (NICE, 2018a) now specify a preferred SSRI. This pathway change is underpinned by recent evidence detailing the side effects of antenatal use of SSRIs on the fetus and neonates (section 1. 3. 2 and 1. 3. 3) and an acknowledgement of the potential effects in contrast to the greater risks of older antidepressant groups.

Although not specifically asked for this study, some of the women in the case group for this study stated that it was often challenging to find the SSRI that achieved good therapeutic outcomes whilst minimising side effects, so this could have driven the SSRI they continued to be prescribed during pregnancy. GP awareness of current prescribing practice and experience with treatment of mental health disorders in pregnancy may also have impacted on SSRI choice especially when national care pathways do not offer specific guidance. Additionally, concerns regarding the dose related effect of citalopram on the QT interval in adults, and particularly women (Vieweg et al, 2012) may have led to only a quarter of the study group being treated with that SSRI (section 4. 7. 1. 2).

Interest in the SSRIs included in the study and particularly citalopram, was expressed from the European Medicines Agency, as part of their pharmacovigilance remit, and the results of this study could be relevant to their organisation, and others. This study was not powered however for subgroup analysis and there is therefore a risk of type I and II error. This was particularly in regard to the citalopram versus paroxetine analysis where only two women had used paroxetine in pregnancy.

The challenges of using SSRIs and prescribing for mental health conditions in the pregnant population could usefully be explored in future studies but are outside the remit of this study and doctorate. A recent meta-analysis (Kohler-Forsberg et al, 2019) built on evidence that SSRIs dampen inflammation processes such as the reduction in cytokines (page 69), by reviewing the effects of various anti-inflammatory medications on depression with positive outcomes. Although none of the stated anti-inflammatory medicines:- ibuprofen, glucocorticoids, minocycline, adrenocortical hormone and statins, prolong the QT interval, they are not safe for use in pregnancy or with breastfeeding. In addition, the FDA have recently licensed the medically supervised use of nasal ketamine for resistant depression (Matthew-King, 2019). Based on very limited human pregnancy and breastfeeding data, a nasal version of ketamine would seem to be potentially safe, however this

data pertains to sporadic use (Drugs.com, 2019). In addition, ketamine has opioid addictive properties which can cause respiratory suppression in the neonate and symptoms indicative of drug withdrawal (Drugs.com, 2019). Hopefully future research will provide the pregnant population with improved medicine management options in regard to mental health. Although this study was specific to SSRIs, health professionals providing evidence-based care to women with complex needs who utilise other forms of medications, may also need to analysis physiology and pharmacodynamics in regard to the neonate, and could undertake studies similar to this.

5. 3. 2 Maternal Mental Health Disorders

The growing incidence of pregnant women with mental health concerns within the total birthing cohort at the DGH is reflected in the increasing requirement for postnatal management plans for the neonate. In 2010, 60 ALERTS were generated in response to antenatal antidepressant use, which had increased to 239 pregnancies in 2017 for SSRI use alone. It is challenging to compare the rate of mental health disorders within the total birthing cohort at the DGH with national (Ban, 2012) and worldwide figures (Hanley et al, 2014; WHO, 2016) when this study purposefully sampled those with a specific pharmacological management. However, one large study of 848,786 pregnant women found 0.49% used SSRIs in the first trimester (Jimenez-Solem et al, 2012), which is comparable with this study (0.39%) despite its much smaller sample size.

The large UK database study by Ban et al (2012) found that the rate of depression and anxiety was greater postpartum then in the nine months prior to pregnancy. Of the 43 case women recruited for this study, 33 (77%) of them were affected by mental health disorders in the period immediately prior to pregnancy, so there is a potential impact on local services for the postnatal period. However, the high rate of pre-pregnancy mental health disorders noted amongst the study group may have resulted from methodological sampling bias.

The NHS Long Term Plan (2019d) seeks to establish maternal medicines networks so that there is access to specialist advise and care throughout pregnancy. At the same time, community hubs will be developed to provide antenatal and postnatal support and advice, which will include a remit for mental health (NHS UK, 2019d). There is also an intent to increase access to perinatal mental health care, increase the underpinning evidence base, and increase the access to CBT and maternity outreach teams (NHS UK, 2019d). In addition, women can also access free, self-help, mental health applications from the NHS Apps Library (2019e). When these aspirations come to fruition, this will provide professionals and women alike with a contemporaneous and streamlined pathway for best practice and care with regards to mental health concerns and the care of the neonate. This aligns with the World Health Organisation (WHO) mental health action plan 2013- 2020 (WHO, 2013), which seeks to establish integrated and responsive care. The need for medicinal treatment of mental health problems may be deferred by more pastoral measures, such as online peer support, mindfulness training, exercise regimes/ yoga and creative activities such as adult colouring, that are may not be readily available to all. In addition, where needed, the use of SSRIs may then be considered and appropriately evidence based. The need to provide greater treatment options for those with perinatal mental health problems has also prompted Health Education England to develop an occupational therapy programme specifically for professionals working within this area (Smith, 2019).

Mental health problems are not confined to the pregnant and postnatal population. Healthcare models being developed for this study's population, have already been applied to elderly mental health services (Burns et al, 2019) and those for the emergency department (NHS England, 2018). Integrated and holistic approaches are being provided in hubs with care delivery happening in the areas of most need. Community teams provide outreach mental health services for care homes and teams with mental health training are triaging those attending the emergency department and utilising appropriate mental health care pathways.

This study sits therefore within this climate of improvement and worldwide initiatives, and adds to the body of knowledge with regard to SSRIs and their effect on the antenatally exposed neonate. In addition, as this study is part of a doctorate, it also increases links between the university and clinical settings with regard to mental health research, and this link is endorsed by WHO (2013).

Whilst this study was not powered to examine these two secondary outcomes or other unexpected findings, the next section considers two interesting birth outcomes that the study found in regard to mode of delivery and mode of feeding.

5. 4 Noteworthy Birth Outcomes

5. 4. 1 Mode of Delivery

Whilst the mode of delivery for the total birthing cohort at the DGH was comparable to the national rates that occurred within the study timeframe, the mode of delivery rates for the case and control groups were not. Nationally in 2016- 2017, 59.4% of women achieved a normal vaginal delivery, 12.7% were delivered by instrumental methods and 27.8% were delivered by Caesarean section (NHS Digital, 2017). 61.1% of the 6620 pregnant women in the total birthing cohort at the DGH, achieved a normal vaginal delivery, with 9.1% and 29.8% being delivered by instrumental methods and Caesarean section respectively. So as a whole cohort the rates were similar to national rates. The case group had a rate of normal vaginal deliveries which was close to national levels (n=23; 53.5%), however the controls had a much lower level (n=17; 37.8%) (section 4. 8. 2). The instrumental rate in the case group was lower than the national average at 7%, however the instrumental rate for the control group was over twice the national average at 28.9% (section 4. 8. 2). Both the case and control groups had higher rates of Caesarean section than the national average, being 39.5% and 33.3% respectively (section 4. 8. 2).

The reasons for the differences between the case and control group versus the national and DGH data is likely to be multi-factorial. Norby et al (2016) stated that women who used SSRIs antenatally tended to be older and have a higher BMI. Indeed, the case women in this study were on average older than the controls (section 4. 5. 1). Advancing maternal age and a higher BMI could trigger enhanced surveillance in pregnancy alone and increase intrapartum interventions, but maternal mental health disorders & anxiety itself could also lead to higher rates. Indeed, the case group in this study had more ultrasound screening for fetal concerns than the controls (section 4. 8. 1). Although the main mode of delivery for the case group was normal vaginal delivery (n= 23), there was still a high proportion of birth by Caesarean section (n=17; 39.5%). Concerns for fetal wellbeing in the case group may have prompted surgical intervention and given rise to delivery rates via Caesarean section that were higher than both the national average and in the control group (n=15; 33.3%). Rubertsson et al (2014) also found that anxiety symptoms in pregnancy tripled the fear of giving birth (OR 3.0; CI 1.9- 4.7) and nearly doubled the preference for a Caesarean section as the mode of delivery (OR 1.7; CI 1.0- 2.8). The higher rate of normal vaginal delivery seen in this study's case group could have been partially due to the proportion of case group neonates (n=27; 63%) who delivered between 37- 39 weeks gestation. Even though research suggests that women with mental health concerns are more likely to have fetal distress in labour (RR= 6.0; 1.88- 19.8) (Davis et al, 2007) and give birth by Caesarean section (OR= 1.74; 1.30- 1.51) (Reis et al, 2010), the greater incidence of birth before their expected date of delivery seen in the case group may have superseded any elective plans for Caesarean section at 39 weeks gestation and post mature fetal complications.

80% of the control group had no fetal concerns on antenatal ultrasound so would not have received extra screening as a result and therefore reduced the potential for early delivery intervention (section 4. 8. 2). Therefore, a greater proportion of the control group delivered at or after their expected date of delivery (n=21 (47%) (control) versus n=17 (40%) (case)), with its associated larger birth weight (mean weight = 3.410kgs (control) versus 3.33kgs (case)) and potential for less postnatal

neonatal problems (section 4. 9. 1; 4. 9. 3; 4. 9. 4). The control group were however chosen due to their requirement to be resident in hospital at 48 hours old as their neonates had a theoretical risk of sepsis, as all completely low risk deliveries would have been discharged at six hours of age. Most treatment was instigated because of maternal triggers and peripartum factors which could prolong labour and also could precipitate an instrumental delivery or Caesarean section (Galal et al, 2012; Knowles et al, 2015). Indeed, only one of the Caesarean section deliveries in the control group was elective versus seven in the case group, with all the other Caesareans being triggered by pathology (section 4. 8. 2). This selection bias may therefore have affected the percentage of neonates recruited to the control group that were delivered by the various modes. Although not the ideal comparison group, a pragmatic approach with ethical consideration and clinical confirmation of wellbeing, meant this was the only way to do this study. Whilst there were generally low rates of normal vaginal deliveries noted, there was no theoretical reason to believe that this impacted on the QT intervals of the neonates in this study especially as no prolongation resulted.

In order to reduce the stillbirth rate, the Saving Babies Lives care bundle (NHS UK 2019c) supports increased antenatal ultrasound scanning of at-risk women, which would apply to the case group women and potentially some of women in the control group. As a result, this increase in surveillance may precipitate a greater proportion of deliveries by surgical or instrumental methods. The proportion of Caesarean section and instrumental deliveries seen in this study may therefore reflect a shift in obstetric practice to greater rates of intervention as a biproduct of this care improvement strategy.

5. 4. 2 Feeding Preference

More than double the percentage of case group neonates (n=16; 37.2%) were artificially fed versus the controls (n=7; 15.6%) (p=0.03*) (section 4. 9. 4. 2). The reason for this is likely to be multi-factorial. Maternal mental health concerns may

have impacted on breastfeeding rates in the case group, and NHS UK (2018) state that SSRIs are not usually recommended with breastfeeding, as they can be transferred in breastmilk to the neonate (Di Scalea et al, 2009). However, for those who choose to breastfeed, Sertraline is considered the best treatment option with fewer effects on the neonate (NICE, 2015). Sertraline is 98% bound to plasma proteins (Cuomo et al, 2018), so the concentration of transferred sertraline in breastmilk is less than 10% of the maternal serum concentration (Pinheiro et al, 2016). In addition, there are several pathways by which the medication is metabolised in the neonate which reduces, although does not eliminate, potential neonate effects (Pinheiro et al, 2016). Nearly half of the case group women (49%) used sertraline, yet breastfeeding rates (n=17; 39.5%) were similar to the artificial feeding rate (n=16; 37.2%), indicating that current pharmacological advice regarding specific SSRI use with breastfeeding was not the only factor in feeding choice (section 4. 9. 4. 3). However, those women who used an SSRI with a lower maternal serum concentration transfer rate in breastmilk (n=16; 59%), were more likely to breastfeed than those using citalopram or fluoxetine which have a higher transfer rate (n=11; 41%) (Field, 2008) (table 4. 26), potentially highlighting awareness of possible impact on neonate from breastmilk ingestion. The maternal medicines networks and community hubs (NHS UK, 2019d) may help improve breastfeeding rates by sharing of gained knowledge from research and good practice.

Supportive feeding measures such as mixed feeding may have been implemented in neonates with antenatal SSRI exposure as they were more likely to be jittery (n=8; 18.6%) than the control group neonates (section 4. 9. 4. 1). Whilst jitteriness is a potential sign of toxicity from antenatal exposure to SSRIs or withdrawal symptoms, it is more commonly a sign of hypoglycaemia which has been found to more prevalent amongst those with antenatal SSRI exposure (RR= 1.61; 1.15-2.27; Davis et al, 2007) (OR=1.56; 1.36- 1.79; Reis et al, 2010) and requires substrate management. Mixed feeding may also have been implemented due to lactation delay (Hurst, 2007) as a side effect of delivery by Caesarean section

(section 4. 9. 4. 3). Lactation and choice of feeding in both groups may also have been affected by concerns for neonatal wellbeing.

Whilst data regarding feeding across both groups were of interest, feeding intention was not ascertained as part of this study, and the study was not powered for assumptions with regard to the neonatal QT interval, especially when the SSRI transfer from breastmilk is expected to be lower than from inutero exposure. However, the article response by Sorlini et al (2013) did find that compared with the baseline mean QT interval for her data on citalopram exposed neonates (n=4), the mean QT interval had increased and was still prolonged within normal parameters in breastfeeding infants at one month of life (p=0.003). Future studies could usefully focus on citalopram particularly and its effects from inutero and breastmilk exposure.

5. 5 Implications for Sudden Infant Death Syndrome

Although different Serotonin neuroreceptors and proteins develop at various points in gestational age, and therefore disruption at key developmental times in embryologic development and maturation may impact on vital organs including the cardiac system (Dubnov- Raz et al, 2010), this has not been demonstrated in this study with regard to antenatal exposure to the SSRIs and the neonatal QT interval.

As SIDS is multifactorial, it is more likely that the Saving Babies Lives care bundle (NHS UK, 2019c) could have more impact on mortality rates for SIDS than the data from this study, as it addresses known factors. If both parents smoke it increases the risk of SIDS by 3.5 times versus non-smokers, or if one parent does, it increases the risk by 1.5- 2 times (The Lullaby Trust, 2018). The Saving Babies Lives bundle (NHS UK, 2019c) actively seeks to reduce smoking in pregnancy and in the partner, so addressing this known risk factor, as well as improving fetal growth from no exposure to nicotine and its associated impact on the placenta. Low birth weight (The Lullaby Trust, 2018) and late or no antenatal care is also

implicated with SIDS, so the enhanced package of care and surveillance that the Saving Babies Lives bundle (NHS UK, 2019c) provides for at risk pregnancies may also impact on rates. The maternal medicines networks and community hubs (NHS UK, 2019d) could also lead to an improvement in breastfeeding rates for this group of women, and breastfeeding reduces the likelihood of SIDS by 60% (The Lullaby Trust, 2018).

SIDS whilst thankfully a rare event, remains an important scientific challenge to overcome. Current research between a group of UK neonatal, paediatric, cardiac, pathology and genetic Consultants, along with Professor Schwartz are examining the prolongation of the QT interval by a genetic mutation (The Lullaby Trust, 2019). Whilst not specific to SSRIs, research related to the QT interval remains an important aspect of the pathology profile.

5. 6 Implications for Future Research

In line with the WHO mental health action plan (WHO, 2013), funding for research has been allocated to mental health services as part of the core NHS performance metrics (NHS UK, 2019d) and could help develop antidepressants with equal or greater efficacy but lesser fetal effects for those who require medicine management. Alongside this work, Academic Health Science Networks (AHSN Network, 2017) are catalysing innovations and research into clinical practice, around best practice and the optimisation of medicine management. Online platforms could also provide a potential catalyst, with the opportunity for worldwide shared learning, through the use of methods such as webinars and research depositories. In addition, the National Institute for Health Research (2019) is galvanising user and professional engagement in all research through the use of the hashtag #BePartofResearch project. Students doing cultural degrees have already utilised social media for their dissertations, and polls are posted to create conversations around clinical questions. This study only utilised online services to

generate the ethics & DGH application form, and for access to statistical analysis software, but in the future, research could usefully utilise online platforms for the research itself.

Social media has not only reported the deaths of cultural figures on television and from music culture as a result of mental health problems, but has started the conversation regarding support and treatment options. The heightened awareness provided by these platforms could help to destigmatise mental health problems, and encourage those struggling mentally to share their issues more readily. Recently, social media has inspired national campaigns to raise awareness of mental health problems in the neonatal unit (Leosneonatal.org, 2019), and for new mothers (maternalmentalhealthalliance.org, 2019). The former campaign utilised data gained from an online survey of parents who had used neonatal services (thesmallestthings.org, 2019). These parents developed anxiety and post-traumatic stress disorder, struggled to get peer support from friends and family due to the different postnatal course they had experienced to others, and grieved for the well-baby they expected to have at term. This awareness week also highlighted a need for health professionals to also be mindful of their own mental health in order to provide appropriate, supportive care. The other UK campaign (maternalmentalhealthalliance.org, 2019) utilised Facebook live sessions to raise awareness of peer support and self-care as well as breastfeeding whilst using antidepressants. A further campaign is focused on general mental health awareness (mentalheath.org.uk, 2019).

As with any change in practice, balancing measures may present themselves along with the improvement. The Saving Babies Lives care bundle (NHS UK, 2019c) which seeks to reduce smoking in pregnancy, could also impact on the availability of future research participants who are pregnant smokers with mental health problems. This potential problem could also present with other quality improvement measures.

5. 7 The Strengths and Limitations of The Study Method/ Methodology

5. 7. 1 Methodology and Methods

The study used an observational study design as it is an exploratory method for clinical practice-based research, where little is known (Singh, 2007). A positivist philosophical framework remained an appropriate methodology on which to answer this research question. A case-controlled method was thought to be the most scientifically appropriate approach for this study. In the absence of an RCT, a longitudinal prospective or retrospective cohort study could have been considered but would not have provided a comparison group, and the research question would not have been answered in the best methodological way. Without a comparison group, the effects of the variables other than the independent variable would not have been addressed, causing uncertainty with regards to the validity of the results.

The choice of the characteristics for the study group participants was guided by the research question and the need for a proxy control group who would be available to have an ECG at 48- 72 hours of age and where there was no indication of a higher risk of a prolonged QT interval. No other group of clinically well neonates were available to provide the required comparison group. Any alternative study strategies would present challenges to sample size, recruitment, generalisability, and validity in answering this research question.

5. 7. 2 Recruitment Process

Based on the data gained in the Dubnov-Raz et al (2008) study, the necessary sample size to achieve 80 % power was calculated as 121 neonates in both case and control groups. The 18 months' timeframe for data collection was set to recruit the required sample size that meet the inclusion and exclusion criteria for the study within one demographic location. Based on data from ALERTS generated in 2014- 2015, there was expected to be 180 antenatally, SSRI exposed neonates

within that timeframe and allowance was made for women who may decline to participate in the study. However, retrospective data from February 2016- August 2017 demonstrated that during the study period there were only a total of 142 women that met the criteria for the study. Whilst a large proportion (81%) of these potential case group participants were considered for this study (n=115), the actual number of potential study participants was less than predicted, and the required sample size would have been a challenge to achieve, although ascertainment bias was probably minimised. It would not have been possible to have calculated or predicted the level of each inclusion and exclusion parameter that occurred prospectively, as there are too many variables, and it is outside the scope of this thesis. However future researchers should be aware of the rate of prematurity, antidepressant prescribing practices, rate of maternal substance misuse and provision of language services in the anticipated research participation sites. Although equal sample size was achieved between the two study groups in this study, consideration would also need to be given to the rate of extended antibiotic therapy in participation sites if the same proxy control group were used.

With hindsight, the limitations of the Dubnov-Raz et al (2008) study should have been noted earlier when utilising their study data for the sample size calculation of this study. However a pragmatic approach was taken, with statistical advice, on its use to calculate sample size for this study, as it was the best data available despite its limitations. Future studies will now have the use of better data to inform their sample size as a result of this study, so further research will not have to take such a pragmatic approach.

Ideally a longer timeframe would have provided the opportunity for greater recruitment and also negate seasonal impact of neonatal sepsis (Eber et al, 2011) and mental health concerns (NHS UK, 2015), but this was not feasible due to clinical and academic constraints. Also, study fatigue noted in prolonged research studies could potentially have then impacted more on recruitment (Patel et al, 2003). In addition, it was anticipated that planned changes in clinical care for those neonates exposed to antenatal SSRIs and being treated for suspected sepsis,

could have been implemented during a longer timeframe and recruitment may have been adversely affected.

A higher percentage of potential case compared to control group women declined to participate in this study (n=15 (13%) versus n=25 (7%)) (section 4. 3. 1 and 4. 3. 2). However, across the study more women agreed to participate than the national average (national decline rate=15- 36%) (Davis et al, 2007; Ramos et al, 2007) for studies involving children, and the rate was within the local maternity decline rate of 0- 22%. The decline rate in the maternity unit was lowest when the women and their neonates derived direct benefit from research participation, such as cervical screening for premature birth. This study's comparatively low decline rate of 7-13% could have been due to altruistic behaviour, or reflected a desire to allay feelings of guilt or fear for their neonate, due to exposing their neonate to SSRIs or indeed when the neonate required antibiotics as a consequence of maternal or intra-partum factors.

Although the recruitment strategy to maintain parity was not always feasible as service and individual processes hindered sequential recruitment, this did not greatly impact on recruitment, and equal sample size was achieved overall. There was only one occasion during the data collection period where recruitment was held for two weeks but that was only in regard to the control group. Late consideration was given to recruiting any potential participant as they occurred, as there was potential for greater recruitment to the control group despite the high rate of extended antibiotic therapy. However, even with three times the number of controls to case group participants from that point, the probability of correctly rejecting the null hypothesis would have only increased from 45% to 62% and still would not have reached the planned 80% power. The burden for the extra potential control participants, with no substantial increase in validity, was thought unethical and not considered further. Had this ratio of recruitment been utilised from the start of the study a larger sample size may have resulted. This, however, would have been a massive challenge for the research team with a clinical

workload, considering the large numbers involved, and the lack of adequate team members until six months into the study. The availability of a funded, research team with no clinical duties would have been needed to have achieved this. Such a team would also have overcome the loss of recruitment that occurred when clinical workload was prioritised (section 4. 3. 1 and 4. 3. 2). Ethically it is important for studies to achieve sample size to provide valid and generalisable data as well as legitimise participation of the study participants, but a dedicated research team was not possible within a self-funded doctoral research study.

5. 7. 3 Methods for Calculating the QT Interval

Machine interpretation of ECG values has been found to be as accurate as manual interpretation by a Cardiologist when results are normal (Smulyan, 2018; Willems et al, 1991). However, where there are abnormal ECG findings, an ECG machine has an increased likelihood of error in interpretation (Smulyan, 2018). Therefore, best practice supports the manual checking of all ECG machine tracings (Smulyan, 2018; Willems et al, 1991) as conducted during this study. The manual generated QT intervals also underwent intra-rater correlation to confirm validity of the original manually read QT intervals. These methods of QT assessment underwent compariability testing and were for the most part within the limits of agreement. All values were less than 440 milliseconds, and mostly within +30 milliseconds of the mean. To standardise and simplify the process, a QT interval calculator (ECG Pedia. Org, 2010a) (appendix J) was used instead of a QT interval reference table (appendix K). This calculator may have over-estimated the value of the QT interval and accounted for the manual readings being generally greater than the ECG machine values. However, when 10% of the QT intervals were re-calculated using the QT interval reference table (appendix K), the results were also generally greater than the ECG machine value. This difference may be due to the manual calculator methods rounding up or down to the nearest ten msecs rather than using the actual value for the calculation. In addition, each square on an ECG is one millimetre wide and equates to 40 milliseconds, so a minuscule difference in assessment can also impact very slightly the obtained

values used for the calculator or reference table. Due to the level of agreement gained when the methods of calculation were compared, all methods of QT interval assessment would have led to the same clinical decisions being made and are therefore comparable methods to have used within this study.

Although not recorded for the purpose of this study, further validation of QT interval normality was gained through the checking of all ECGs by a Neonatal Consultant, which found the QT interval values were in accordance or similar to the primary manual measurements. Repeated measures by the above strategies substantiated the QT intervals obtained and validated their normality. Another strategy could have included a blinded inter-rater check of the QT interval, however as validity was ascertained with the above strategies, this was not undertaken.

This section has demonstrated that while a prospective, case-controlled study, with improved rigor in relation to other published data (Dubnov-Raz et al, 2008), has been undertaken, it has not been without its challenges. Strategies to improve recruitment within a self-funded research study were not feasible, and although similar recruitment numbers to the Dubnov-Raz et al (2008) study were achieved, this study was ultimately underpowered. The sample size calculation was based on data (Dubnov-Raz et al, 2008) that was disparate to the findings of this study, and as such may have produced an error in estimating the appropriate sample size for achieving 80% power. The timeframe proved to be both inadequate and a challenge for sustaining recruitment. The validity of the methods of interpretation for the QT interval were however confirmed.

5. 8 Summary of Discussion

When faced with the challenges of a longitudinal study in the clinical setting, a pragmatic approach was required for several aspects of the research study, especially in regard to recruitment. Several strategies were considered and implemented in order to improve study recruitment when faced with competing priorities, clinical workload and recruitment fatigue, in the absence of an independent research team. Such strategies were framed by the method, methodology and research question for the study, but were unsuccessful in achieving the required sample size. The study has however provided new insights into the challenges of achieving sufficient sample size when so many potential participants fulfil one or more of the exclusion criteria, and highlights that a proxy comparison group may have its own challenges to recruitment, which need consideration.

The effect of exposure to antenatal SSRIs on the neonatal QT interval did not reflect other published papers, and this was potentially due to this study method and improved rigor in this study in regard to the inclusion and exclusion criteria. The sequential increase in the use of SSRIs in the population delivering at the DGH highlighted a growing demand for mental health support services, and these should be achieved through the implementation of the NHS Long Term Plan (2019) and WHO (2013) recommendations. Collaborative clinical networks and research in mental health should strive to find an individualised treatment plan for those affected by these conditions, and provide a clear management strategy for the pregnant population. Lessons learnt from care improvements for the study population, could be usefully utilised by other areas of mental health care, working towards improvements in mental health throughout a lifetime. The final chapter discusses the implications of the results and research journey on future clinical and personal practice, as well as making recommendations for future research.

6 Conclusion

6. 1 Introduction

This doctoral study was driven by the need to provide support and information to women utilising SSRIs in pregnancy and their neonates. This need informed the research question which sought to ascertain whether there is an association between antenatal exposure to SSRIs and a prolonged QT interval in the term neonate at 48-72 hours old. Whilst this study is underpowered due to sample size, it has added to the body of knowledge regarding the effect of antenatal SSRI exposure on the neonatal QT interval and represents one of two of the largest collection of data regarding this research question. This study found no neonates with a prolonged QT interval after antenatal exposure to SSRIs, and as such presents research that challenges the findings of other published studies (Degiacomo et al, 2016; Dubnov et al, 2005; Dubnov-Raz et al, 2008). Although slightly smaller sample size then the only other case- controlled study (Dubnov-Raz et al, 2008), this study demonstrates greater rigor and applicability to the current SSRI prescribing patterns in the UK.

This final chapter of the thesis starts with a reflection on the implications of the study results for clinical and personal practice as well as the implications for education. Recommendations for future research are then detailed, and finally how the findings of this study have and will be disseminated are discussed.

6. 2 Implications for Clinical Practice

6. 2. 1 Implications for Clinical Practice Related to the Study Process

As there was no prolonged QT intervals noted on the ECG of antenatally SSRI exposed neonates, no changes to the local clinical care pathway have been made

in response to this study's findings, and an ECG is not routinely offered to this population as part of postnatal management.

However, the study has impacted on care delivery within the study setting in other ways through enhanced evidence-based and consistent care. Guidelines for the immediate care of the new-born, care of a neonate with a prolonged QT interval (appendix K) and interpretation of the ECG of a day 2 neonate (appendix J) were generated, in addition to contemporaneous postnatal plans. Enhanced care has resulted from staff participation and training in the ECG service that the maternity unit provide, and has been commended by other areas in the DGH.

A gap in clinical care was highlighted in a national study (Thomas et al, 2017) which found that only four neonatal units in the England had a protocol for the management of neonates with antenatal SSRI exposure. The data and literature review provided within this thesis could therefore usefully inform guidance produced by other hospitals for their own population.

Coincidentally, this study highlighted the periodic increase in extended antibiotic therapy, and this indirect research finding was discussed with a Consultant Microbiologist. With the advent of the NICE guidance on the treatment of early onset neonatal sepsis with Benzylpenicillin and Gentamicin (NICE, 2012), it is key that pathological sciences are aware of and can assess the impact of current treatment strategies on current and future health, as well as the bacterial climate of the environment the neonate and the women are cared within. These findings informed this surveillance process, and also highlights how clinical research can benefit care outside of the study focus.

6. 2. 2 Implications for Personal Practice

Undertaking this doctorate and associated research has developed my understanding and knowledge regarding the process of undertaking a clinical

trial. I have gained experience in the use of new systems and have a greater understanding of the requirements of the different regulatory bodies. I have also gained a greater knowledge in the development of patient and research documentation that meets ethical, patient and GCP requirements. Academically, I have a greater understanding of the development of a doctoral thesis and have gained some understanding and experience of the requirements needed to publish an academic paper. I have developed links with the research community with the maternity unit, the DGH and the patient safety network for the region, and have been able to share my knowledge as well as actively engage with ongoing research and service development as a result. Personally, I will incorporate lessons learnt from the challenges of undertaking a research project and academic award whilst working full time clinically. Research in the clinical area is an amazing opportunity to make key improvements to care, however future projects will be need appropriate allowance of time and appropriate staffing.

This thesis and research study has also provided me with an increased knowledge of the effects of SSRIs on both the neonate and the woman, and allowed me to incorporate this into my daily clinical practice as well as apply it to the ALERTS that are generated for postnatal care of the neonates. This increased knowledge also underpins the general guidance I provide regarding the immediate care of the new-born in the maternity unit. Though not part of the data collection for this study, the conversations I had with the case group women also gave me insight into their lived experience as women with mental health disorders. Some of this knowledge may usefully be applied to future projects on this subject.

6. 2. 3 Implications for Education

The updated guidance for the postnatal care of antenatally SSRI exposed neonates developed as a result of this study, has now become imbedded as standard care at the DGH. New staff will be informed of this guidance and updates for all staff will be provided as required, so that women receive consistent and

evidence-based information from all health professionals at the DGH. The literature search and research findings have been shared with medical students who had a placement on the neonatal unit prior to a period in a mental health setting. This increased their awareness of concerns with regard to pregnant women with mental health problems, and also their knowledge and interest in the subject area. Further sessions will be provided for other medical students on the same pathway. As staff participation in this study has created an awareness regarding research processes, these skills can be developed and utilised for future service development, which is a current key national directive, as well as meet the professional responsibility to undertake best practice (Nursing and Midwifery Council, 2015). This learning can then be shared with their peers. More education could also usefully be provided to General Practitioners, who are faced with the challenges of an increasing mental health burden and a perinatal mental health framework that lacks guidance on specific SSRI use in pregnancy.

6. 3 Recommendations for Future Study

6. 3. 1 A Greater Resourced and Larger Scale Observational Study

Although the required statistical power was not achieved, this study can evidence whether further research on this topic is warranted and also the feasibility of recruitment for a larger, well-resourced observational study. Given the findings of the current study and enhanced awareness of methodological deficits of previously published work, great consideration would be needed as to whether a larger scale observational study would be best practice.

A large and fully resourced research body could achieve an appropriately powered study with a large sample size through the provision of dedicated research staff working across multiple research sites (Gul et al, 2010). In addition, a very large sample size would allow for stratification of the data by SSRI type, by dosage of SSRI, and by gestation at ingestion, for greater validity and transferability to the

wider neonatal population in regard to the effects of antenatal exposure to SSRIs on the neonatal QT interval.

Consideration would need to be given to the timing of the ECG screening and the location given the recent clinical pathway change for the postnatal care of the antenatally SSRI exposed neonate. Whilst the recommendation continues to be that these neonates remain in hospital for 48 hours of observation, if certain criteria are fulfilled then they may be discharged home prior to that time, and as such would not be resident in hospital at 48-72 hours of age for an ECG. Consideration of undertaking research ECGs in a community or outpatient setting would potentially be required, and cost implications would also be a factor, as additional pathways would be required for professional consultation for interpretation and follow up management. The use of wireless handheld technology with online access to a health professional for review may precipitate a more coherent pathway.

The choice of control group neonate would also require further consideration. Post-study clinical changes to the neonatal suspected sepsis pathway mean the study cannot be replicated with the same criteria for the control group within the hospital environment. However, if the need for a hospital resident is removed by surveillance after discharge, then the need for a proxy control group would also be negated. Fit and healthy neonates with no postnatal concerns could be recruited to the research study at delivery and have ECG screening in the community or outpatient setting. There would be an associated time and financial burden on the family who participate, but a well-resourced research body could offer compensation for this if required. Equally, such a research body could potentially provide ECG machines that are robust enough for screening in the community and funded staff to attend the families at home. If the research study was replicated in a community setting, further consideration would have to be given to the timing of the ECG, and whether a wider age parameter would be of value, as well as acceptable to the parents.

However, as it has already been discussed based on the results of this study, a potential sample size probably in the order of tens of 1000s could be required, and pragmatically that level of screening would not be a cost-effective option in a cost pressure restricted NHS service. Funding and time that could arguably be better spent on prioritising care in regard to other areas relating to the neonatal cardiac system, or PPHN where there is a known greater risk of morbidity and mortality. Equally funding could be used to develop promising new antidepressants with similar efficacy but fewer fetal and neonatal effects as discussed in section 5. 3. 1 or support the work of perinatal community hubs (section 5. 3. 2). Further, a pragmatic and appropriate assessment of neonates with SSRI exposure, could alert clinical staff to those with potential risk factors in addition to SSRI exposure, such a family history of sudden death or SIDS, and the judicious use of ECG screening could be applied. If further research suggests that there is an association between antenatal SSRI exposure and a prolonged QT interval in the neonate, then this research question could be re-examined and actioned as above within the context of clinical practice at that time.

6. 3. 2 Qualitative Exploration of the Lived Experience of Mental Health in Pregnancy

During the completion of the study datasheet, the women talked freely about what had triggered their mental health disorders. This data was outside the scope and focus of this study, but was an interesting insight. Most expressed concern that their neonate had been exposed to SSRIs but recognised and were reassured that stable mental health was important for mother and baby, and long-term outcomes. A future study could usefully build on previous qualitative perinatal mental health data with an exploration of the lived experience of a purposefully selected group of women with mental health concerns at the DGH. This knowledge could further enrich the care these women and their neonates receive and provide further evidence for the postnatal care (section 3. 2. 2) detailed in the neonatal ALERT (appendix A).

6. 3. 3 Qualitative Exploration of Research Engagement Among Maternity Service Users

Conversing with the women during the undertaking of this study provided an interesting and informal insight into their rationale for engaging with the research process. In common with the Meshaka et al (2016) study exploring why pregnant women take part in clinical trials, several of the women in the case group verbalised that they were glad that research was being undertaken in an area that was pertinent to themselves. Some also expressed that they felt there was a lot of uncertainty about the use of SSRIs in pregnancy and welcomed both the study and the knowledge their participation could provide (Meshaka et al, 2016). Data on research engagement amongst maternity care users is however limited and therefore could be usefully explored in future research. Meshaka et al (2016) utilised a cohort from an on-going maternity research study, and this framework could be adapted to the population at the DGH as there are several studies involving maternity service users currently recruiting.

6. 3. 4 Other Potential Research

Although the normal target blood level values are known for older antidepressants such as tricyclic antidepressants (Linder et al, 1998), they are not known for SSRIs. In view of the recommendation to treat pregnant women with mental health problems with the lowest dose of SSRIs that provide efficacy (*[local area] NHS UK, 2016), a study on this topic could usually provide data to guide this recommendation.

Breastfeeding is important for the transfer of secretory immunoglobulin A and lactoferrin which are key components of a neonatal immune system (Hanson et al, 1981). Breastfeeding also promotes bonding between mother and baby which is important for future emotional, social and physical development for the neonate.

This bonding is especially important when the mother also has a mental health disorder. However this study has demonstrated that SSRI medicated women may be conflicted in their feeding choice, and this could be due to the lack of large-scale robust data on the levels of SSRIs in breastmilk. Data are based on small numbers (n= 11- 55) of lactating women using the four SSRIs reported in this study (drugs.com, 2012a; drugs.com, 2012c; drugs.com, 2012e; drugs.com, 2012f). Paroxetine has been reported in breastmilk at 1.2% of the maternal weight adjusted dose (drugs.com, 2012e), however the range stated for citalopram (drugs.com, 2012a) and fluoxetine (drugs.com, 2012c) is between 5.9% of maternal weight adjusted dose to a quarter of the maternal serum concentration. A large-scale research study with standardised measurements could usefully provide improved data so that women who are using SSRIs and wish to breastfeed, will be better informed regarding their feeding choice.

As the NHS undertakes digitalisation, databases generated could be comparable to the large databases seen in section 1. 3. 4. 1. There could then be an opportunity for large scale studies to utilise these databases in regard to the pregnant and postnatal population, as well as for the general population with mental health problems.

6. 4 Dissemination of the Study Findings

It is important that the study findings are shared with the wider community to validate the participation of the women and neonates, to increase the body of knowledge on the topic and prevent unnecessary replication. The research study and its findings will therefore be used in the generation of a paper for publication. An additional paper will utilise the literature review to create an evidenced based management strategy for the postnatal care of SSRI exposed neonates, and hopefully address the lack of guideline for this population in UK neonatal units.

As publication is not the only means of dissemination to the academic and clinical community, this study has been presented at conference by means of an oral presentation to the postgraduate students and staff at the University of Southampton. The personal research journey has been presented to the Linking Education and Research in Neonates (LEARN) Neonatal Nurse Association group. This was well received and prompted engagement with another member who was involved in SSRI research focusing on congenital abnormalities. Further conference presentation of the study will be considered after the publication of the above papers.

All participating families were offered an update on the study findings after the study was complete. This communication thanked the families for their participation in the study, notified them that the study had now been completed, that 88 babies received an ECG, and that no abnormalities regarding the QT interval were found in any of the babies. One email recipient replied that she was pleased that they had participated in the study. Participants were also reminded that the study findings would be shared within the DGH and nationally.

The neonatal and maternity staff at the DGH have received feedback on the study findings, and the results were shared in the neonatal unit's newsletter. The study was also included in the Practice Development Unit updates where improvement practice is showcased. After the thesis is complete, the study findings will be shared via the Trust wide bulletin and displayed on the hospital notice board where staff and patients outside of maternity can view it.

6. 5 Concluding Comments

This research study and thesis have been the result of eight years of academic and clinical application. It has been a challenging and enlightening process which has shaped both clinical practice and personal aspirations. It has provided the knowledge and confidence to engage with health

professionals and advocates regarding this doctoral journey, as well as evidencing and leading on quality improvement to promote evidence-based neonatal clinical care.

This prospective study modified the approach taken in a previous study in a number of significant aspects to increase rigor and therefore validity with regard to antenatal SSRI use and the QT interval of the exposed neonate. This study has demonstrated that this area of exploration is now less of a priority for future research than other issues in the care of women using SSRIs in pregnancy and their exposed neonates. With increasing mental health awareness and therefore the need for therapeutic management strategies, it is important that funding for research is allocated appropriately, to provide optimal cost -benefit options, especially for this population. It is hoped that the NHS Long Term Plan (2019) and the WHO (2013) recommendation to increase research into mental health management will address this. The findings of this study however do not support the financial and resource outlay a larger study on this specific topic would require. Continued reporting via the yellow card system of any suspected adverse transplacental effects in relation to antenatal exposure to SSRIs remains important (Medicines & Healthcare Products Regulatory Agency UK, 2018). Heightened awareness of pharmacovigilance within the pregnant population could highlight areas for future research. Digitalisation of health care provision could also provide the opportunity to assess large scale data in regard to mental health and pregnancy outcomes. This study has however provided this area of research with a contrary argument of greater validity and rigor, which can be utilised in the pursuit of evidence-based maternity and neonatal care.

Appendix A Neonatal ALERT Form

NEONATAL ALERT FORM

Referral of potential problems identified during the antenatal period

Maternal identification label

Obs. consultant:

Midwife:

Date of referral:

EDD:

Person completing alert:

Potential problem/abnormality identified:

……

……..……

……

Relevant history:

……

……

……

Advice already given to mother/parents:

……

…….……..

Plan for further pregnancy care:

Next visit/review:

Anticipated place of delivery: x □ x □ x □ Other □

To be reviewed □

Anticipated mode of delivery: Vaginal □ CS □ To be reviewed □

Antenatal counselling by neonatal team: Required □ Not required □ To be reviewed □

Plan of neonatal team:

Book for antenatal counselling**: Yes** □ **No** □ If yes, when:

Presence of neonatal team at delivery: **Yes** □ **No** □

If yes, SHO □ ANNP/Registrar □ Consultant □

……

……

……..

Postnatal care:

Entry completed by:

Postnatal Management:

……

……

…….

Antenatal management plan: Fully adhered to □ Partially adhered to □

Not adhered to □

Please return these forms to:

XX, ANNP

Neonatal Alert System Coordinator

Neonatal Unit

X Hospital NHS Trust

X

Tel: X

Fax: X

Please direct any queries/suggestions regarding this system/form to:

Dr. X

Lead Consultant Neonatologist

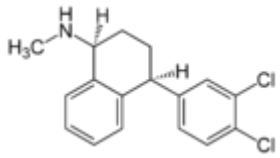
X Hospital NHS Trust

Appendix B SSRIs and Their Properties

B.1 Sertraline

(Zoloft, Lustral, Serlain, Asentra)

B.1.1 Chemical Formula



B.1.2 Use (Drugs.com, 2012f)

Depression

Obsessive-compulsive disorder

Panic disorder

Anxiety disorders

Post-traumatic stress disorder

Premenstrual dysphoric disorder

B.1.3 Side Effects in Adults (Drugs.com, 2012f)

Agitation	Facial paraesthesia
Allergic reactions	Nausea
Angina	Memory problems
Arrythmias	Lack of concentration

Confusion	Headache
Constipation	Alopecia
Dizziness	Seizure
Dry mouth	Stomach pain
Dyspepsia	Withdrawal symptoms
Facial paraesthesia	Shallow breathing/ apnoea
Hallucinations	Sedation
High fever	Loss of appetite
Hypertension	Weakness
Insomnia	Weight loss
Low libido / impotence	Upper GI bleeding
Overactive reflexes	Dystonia
Raised LFTs	Galactorrhea
Rigid muscles	Diarrhoea
Seizure	Increased cholesterol levels
Sexual disfunction	SIADH
Sweating	Worsening or new symptoms of psychological disorder
Tremors	

B.1.4 Reported Effects on Neonate if Use in Pregnancy (Drugs.com, 2012f; Louik et al, 2007)

Anal atresia	Constant crying
Apnoea	Hypotonia
Cyanosis	Difficulty sleeping
Feeding difficulty	Tremor

Neonatal withdrawal symptoms	Jitteriness
Neonatal withdrawal symptoms	Vomiting
Omphalocele	Irritability
Persistent Pulmonary Hypertension of the Newborn	High pitched cry
Respiratory Distress	Hypoglycaemia
Seizures	Hypertonia
Temperature instability	Hyperreflexia

FDA pregnancy category C

B.1.5 Reported Effects if Use with Breastfeeding (Drugs.com, 2012)

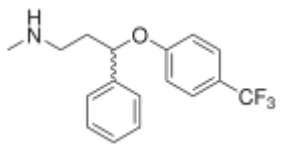
Excreted in breastmilk in small amounts

Benign neonatal myoclonus	Withdrawal symptoms when stopped
Blunted response to pain	Agitation

B.2 Fluoxetine

(Depex, Prozac, Fontex, Seromex, Seronil, Sarafem, Ladose, Motivest, Flutop, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS), Prodep (IND))

B.2.1 Chemical Formula



B.2.2 Use (Drugs.com, 2012c)

Depression

Bulimia Nervosa

Obsessive-compulsive disorder

Panic disorder

Bipolar disorder

Premenstrual Dysphoric Disorder

B.2.3 Side Effects in Adults (Drugs.com, 2012c)

Agitation	Stomach pain
Allergic reactions	Loss of appetite
Alopecia	Hyponatraemia
Arrythmias	Drowsiness
Confusion	Seizure
Diarrhoea	Worsening of pre-existing restless leg syndrome
Dizziness	Sedation
Hallucinations	Weight changes
High fever	Memory problems
Increase risk of suicidal tendencies	Headache
Increased intraocular pressure	Increased risk of fracture of hips
Low libido / impotence	Insomnia
Nausea	Upper gastrointestinal bleeding
Nervousness	Paresthesia
Nightmares	Dry mouth

Overactive reflexes	Increased appetite
Panic attacks	Shallow breathing/ apnoea
Pyrexia	Constipation
Rigid muscles	Lack of concentration
Sexual disfunction	**QT prolongation**
Sexual obsession	**Torsades de pointes**
Sneezing	Increased prolactin
Sore throat	SIADH
Stuffy nose	Altered platelet function
Sweating	Weakness
Tremors	Migraines
Re-activation of Herpes simplex virus	Dyspepsia
Worsening or new symptoms of psychological disorder	Dystonia
Interstitial pulmonary damage	

B.2.4 Reported Effects on Neonate if Use in Pregnancy (Drugs.com, 2012c; Merck Manual, 2007)

Apnoea	Hypertonia
Constant crying	Lower birth weight
Cyanosis	Hypotonia
Feeding difficulty	Jitteriness
Neonatal withdrawal symptoms	Hypoglycaemia
PPHN	Greater miscarriage risk
Preterm birth	Shorter length of body
Respiratory distress	High pitched cry

Seizures	Hyperreflexia
Sleeping difficulties	Structural abnormalities
Temperature instability	Tremor
Vomiting	Irritability

FDA pregnancy category C

B.2.5 Reported Effects if Use with Breastfeeding (Drug.com, 2012c; Merck Manual, 2007)

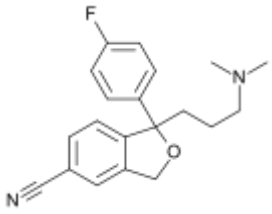
Excreted in breastmilk in greater amounts than other SSRIs

Vomiting	Irritability
Blunted response to pain	Neonatal abstinence syndrome
Colic	Failure to thrive
Glycosuria	Cyanosis
Hyperglycaemia	Seizure
Unknown effects on neonate, maybe of concern	Drowsiness
Watery stools	

B.3 Citalopram

(Celexa, Cipramil, Cipram, Dalsan, Recital, Emocal, Sepram, Seropram, Citox, Cital)

B.3.1 Chemical Formula



B.3.2 Use (Drugs.com, 2012a)

Depression

B.3.3 Side Effects in Adults (Drugs.com, 2012a)

Aggression	Gastric ulcers
Agitation	GI disturbances
Allergic reaction	Dizziness
Alopecia	Nystagmus
Anorexia	GI haemorrhage
Anxiety	Nausea
Apnoea	Cough
Arrythmias	Flatulence
Ataxia	Withdrawal symptoms
Bundle branch block	Transient ischaemic attack
Chest pain	Myocardial infarction
Drowsiness	Weight changes
Dry mouth	Amenorrhoea
Fatigue	Impotence
Galactorrhoea	**Prolonged QTc**
Hallucinations	Jaundice
Headaches	Stuffy nose
Hypertonia	Loss of concentration
Hyponatraemia	Increased cholesterol levels

Hypothyroidism	Epistaxis
Increase risk of fractured hips	Cerebral vascular accident
Insomnia	Sexual dysfunction
Overactive reflexes	Dyskinesia
Prolactinaemia	Pulmonary embolism
Pyrexia	Diarrhoea
Tachycardia	Dermatitis
Seizures	Sore throat
SIADH	Thrombosis
Sinusitis	Angina
Suicidal thoughts	Fainting
Sweating	Dyspepsia
Taste alteration	Eye pain
Tinnitus	Acute renal failure
Torsades de pointes	Anaemia
Tremors	Dystonia
Upper respiratory tract infection	Hypotension
Vertigo	Confusion
Worsening of psychological symptoms	

B.3.4 Reported Effects on Neonate if Use in Pregnancy (Drugs.com, 2012a)

Apnoea	Gastrointestinal disturbances
Feeding difficulty	Hypoglycaemia
Hypotonia	Miscarriage
Respiratory distress	Hypertonia
Seizures	Irritability
Sleep disorders	High pitched cry
Withdrawal symptoms	Tremor

FDA pregnancy category C

B.3.5 Reported Effects if Use with Breastfeeding (Drugs.com, 2012a)

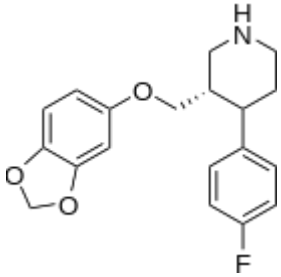
Excreted in breastmilk

Decreased feeding	Withdrawal symptoms
Sleepiness	Weight loss

B.4 Paroxetine

(Paxil, Seroxat, Sereupin, Aropax, Deroxat, Divarius, Rexetin, Xetanor, Paroxat, Loxamine, Deparoc)

B.4.1 Chemical Formula



B.4.2 Uses (Drugs.com, 2012e)

Depression

Obsessive-compulsive disorder

Anxiety disorder

Post-traumatic stress disorder

Premenstrual dysphoric disorder

B.4.3 Side Effects in Adults (Drugs.com, 2012e)

Abdominal pain	Increased cough

Abnormal LFTS	Myopathy
Aggression	Pyrexia
Agitation	Hallucinations
Allergic reaction	Bone pain
Anaemia	Yawning
Angina	Thrombocytopenia
Blurred vision	Increased risk of hip fractures
Chorea	Alopecia
Confusion	Apnoea
Discontinuation symptoms	Rhinitis
Dizziness	Lack of concentration
Dry mouth	Ulcers
Gastrointestinal disturbances	Tremors
Gingivitis	Dyskinesia
Hyperactive	Nausea
Hypertension	Hypothyroidism
Hypertonia	Confusion
Hypotension	SIADH
Insomnia	Flatulence
Lethargy	Mastitis
Loss of co-ordination	Headaches
Palpations	Hyperthyroidism
Panic attacks	Unusual bleeding
Restless	Tachycardia
Sexual dysfunction	Dyspepsia
Sinusitis	Hyperventilation

Skin reactions	Constipation
Stupor	Amenorrhoea
Suicidal thoughts	Weight loss/ gain
Sweating	Seizures
Tinnitus	Altered taste
Urinary tract infections	Hyponatraemia
Worsening of psychiatric condition	Swellings/ bruising
Conjunctivitis	

B.4.4 Reported Effects on Neonate if Use in Pregnancy (Bar-Oz et al, 2007; Bellantuono et al, 2007; Drugs.com, 2012e; Kallen, 2007; Thormahlen, 2006; Way, 2007)

Cardiac defects	Hypospadias
Hypertonia	Irritability
Jitteriness	Cyanosis
Persistent Pulmonary Hypertension of the Newborn	Poor feeding
Respiratory depression	Apnoea
Seizures	High pitched cry
Sleep disturbances	Temperature instability
Spontaneous miscarriage	Atrial Septal Defect
Ventricular Septal Defect	Lethargy
Withdrawal symptoms	

FDA Pregnancy Category D

B.4.5 Reported Effects if Use with Breastfeeding (Drugs.com, 2012e)

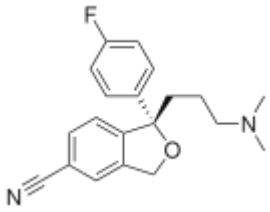
Excreted in breast milk

No adverse effects have been documented.

B.5 Escitalopram

(Lexapro, Cipralex, Seroplex, Esertia)

B.5.1 Chemical Formula



B.5.2 Use (Drugs.com, 2012b)

Anxiety

Major Depressive Disorder

B.5.3 Side Effects in Adults (Drugs.com, 2012b)

Acne	Abnormal gait
Acute renal failure	SIADH
Agitation	Insomnia
Allergic reaction	Headache
Anxiety	Hallucinations
Back discomfort	Dry eyes

Bruising	**QT prolongation**
Dizziness	Tinnitus
Dry mouth	Limb pain
Dry skin	Taste alteration
Dystonia	Dystonia
Gastrointestinal disturbances	Flu symptoms
Hepatitis	Hyponatraemia
Hot flushes	Hypertension
Hypercholesterolemia	Blurred vision
Hypertonia	Abdominal pain
Insomnia	Apnoea
Irritability	Drowsiness
Muscle cramps	Eye irritation
Nausea	Reflux
Palpations	Thrombocytopaenia
Panic attacks	Seizures
Pyrexia	Weight loss/ gain
Raised bilirubin	Dermatitis
Sexual dysfunction	Involuntary muscle contractions
Skin rash	Lack of concentration
Suicidal thoughts	Constipation
Sweating	Flatulence
Tachycardia	Heartburn
Tremors	Toothache
Unusual bleeding	**Torsades de pointes**
Urinary tract infections	Ventricular tachycardia

Vertigo	Carpal Tunnel Syndrome
Vomiting	Gastrointestinal bleeding
Worsening of psychiatric disorder	Confusion
Chest pain	

B.5.4 Reported Effects on Neonate if Use in Pregnancy (Drugs.com, 2012b)

FDA pregnancy category C

No controlled human data available

B.5.5 Reported Effects if Use with Breastfeeding (Drugs.com, 2012b)

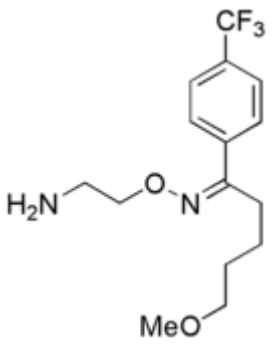
Excreted in breast milk

Weight loss	Poor feeding
Lethargy	

B.6 Fluvoxamine

(Luvox, Fevarin, Faverin, Dumyrox, Favoxil, Movox, Floxyfral)

B.6.1 Chemical Formula



B.6.2 Use (Drug.com, 2013d)

Social Phobias

Obsessive-Compulsive Disorder

B.6.3 Side Effects in Adults (Drug.com, 2012d)

Allergic reactions	Tachycardia
Skin rash	Vomiting
Respiratory distress	Lack of co-ordination
Worsening of psychiatric disorder	Fainting
Anxiety	Hypertonia
Panic attacks	Sweating
Insomnia	Tremors
Irritability	Headache
Agitation	Lack of concentration
Aggression	Dizziness
Hyperactivity	Apnoea
Suicidal thoughts	Sexual dysfunction
Seizures	Yawning
Weight loss/gain	Nausea
Bruising	Muscle pain
Unusual bleeding	Dyspepsia
Extremes of emotion	Dry mouth
Hallucinations	Flatulence
Pyrexia	Abdominal pain
Mania	Constipation
Hallucinations	GI bleeding
Paranoia	Drowsiness
Abnormal dreams	Vertigo
Chest pain	Tourette's Syndrome
Discontinuation symptoms	Hyponatraemia

Anorexia	SIADH
Rhinitis	

B.6.4 Reported Effects on Neonate if Use in Pregnancy (Drugs.com, 2012d)

FDA pregnancy category C

Nil reported human effects

B.6.5 Reported Effects if Use with Breastfeeding (Drugs.com, 2012d)

Excreted in breast milk

Effects unknown but may be of concern

B.7 Dapoxetine

Discontinued

B.8 Indalpine

Discontinued

Appendix C Other Studies Exploring SSRI Exposure in Pregnancy and Effects on Neonates

C.1 Prematurity

Association	Author	Design of Study
Yes (majority)	Udechuku et al, 2010	Systematic review

C.2 Neonatal Abstinence Syndrome

Association	Author	Design of Study
Yes	Kallen, 2007	Literature review
Yes	Pearlstein, 2015	Literature review
Yes	Tuccori et al, 2009	Literature review
Yes	Way, 2007	Literature review
Yes	Yonkers et al, 2009	Literature review

C.3 Cardiac Abnormalities

Association	Author	Design of Study
Yes	Diav-Citrin and Ornay, 2012	Literature review
Yes	Fenger-Gron et al, 2011	Systematic Review
Yes	Ornay and Koren, 2014	Literature review

C.4 Other Abnormalities

Association	Author	Design of Study
Yes- hypospadias	Ornay and Koren, 2014	Literature review
Yes –eye	Udechuku et al, 2010	Systematic review

C.5 Neurological Effects

Association	Author	Design of Study
?	Diav-Citrin and Ornay, 2012	Literature review
?	Koren and Nordeng, 2012	Literature review
Yes- motor developmental delay (young children)	Monk, Fitelson and Werner, 2011	Literature review
Yes- motor developmental delay (young children)	Ornay and Koren, 2014	Literature review
Yes- motor developmental delay (young children)	Pearlstein, 2015	Literature review

?- motor developmental delay (young children)	Yonkers et al, 2014	Literature review

Appendix D Medications That Prolong the QT Interval and May Be Associated with Torsades De Pointes (TdP)

D.1 Medications That Prolong the QT Interval and Have a Risk of Causing Torsades De Pointes

The following medications prolong the QTc and have a risk of causing Torsades de pointes (Azcert.Org, 2013a)

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males, TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males, TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis	
Azithromycin	Zithromax®	Antibiotic / bacterial infection	
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	
Citalopram	Celexa®	Anti-depressant / depression	

Generic Name	Brand Name	Class/Clinical Use	Comments
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Domperidone	Motilium®	Anti-nausea / nausea	
Droperidol	Inapsine®	Sedative; Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	E.E.S.®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	Erythrocin®	Antibiotic; GI stimulant / bacterial infection; increase GI motility	Females>Males
Escitalopram	Cipralex®	Anti-depressant / Major depression/ Anxiety disorders	
Escitalopram	Lexapro®	Anti-depressant / Major depression/ Anxiety disorders	
Flecainide	Tambocor®	Anti-arrhythmic / abnormal heart rhythm	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	

Generic Name	Brand Name	Class/Clinical Use	Comments
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Ondansetron	Zofran®	Anti-emetic / nausea and vomiting	
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sevoflurane	Ulane®	Anaesthetic, general / anesthesia	Label warning for patients with congenital long QT or

Generic Name	Brand Name	Class/Clinical Use	Comments
			patients taking QT prolonging drugs
Sevoflurane	Sojourn®	Anaesthetic, general / anesthesia	Label warning for patients with congenital long QT or patients taking QT prolonging drugs
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis	
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	

D.2 Medications That Have Been Found to Prolong the QT Interval but Whether They Lead to Torsades De Pointes is Inconclusive

The following medications have been found to prolong the QTc but whether they lead to Torsades de pointes is inconclusive (Azcert.Org, 2013b)

Generic Name	Brand Name	Class/Clinical Use	Comments
Alfuzosin	Uroxatral®	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Symmetrel®	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease	
Artenimol+piperaquine	Eurartesim®	Anti-malarial /	

Generic Name	Brand Name	Class/Clinical Use	Comments
Atazanavir	Reyataz®	Protease inhibitor / HIV	
Bedaquiline	Sirturo®	Anti-infective / Drug-resistant Tuberculosis	Black Box for QT
Chloral hydrate	Noctec®	Sedative / sedation/ insomnia	
Clozapine	Clozaril®	Anti-psychotic / schizophrenia	
Dolasetron	Anzemet®	Anti-nausea / nausea, vomiting	
Dronedarone	Multaq®	Anti-arrhythmic / Atrial Fibrillation	
Eribulin	Halaven®	Anti-cancer / metastatic breast neoplasia	
Famotidine	Pepcid®	H2-receptor antagonist / Peptic ulcer/ GERD	
Felbamate	Felbatrol®	Anti-convulsant / seizure	
Fingolimod	Gilenya®	Immunosuppressant / Multiple Sclerosis	
Foscarnet	Foscavir®	Anti-viral / HIV infection	
Fosphenytoin	Cerebyx®	Anti-convulsant / seizure	
Gatifloxacin	Tequin®	Antibiotic / bacterial infection	
Gemifloxacin	Factive®	Antibiotic / bacterial infection	
Granisetron	Kytril®	Anti-nausea / nausea and vomiting	

Generic Name	Brand Name	Class/Clinical Use	Comments
Iloperidone	Fanapt®	Antipsychotic, atypical / Schizophrenia	
Indapamide	Lozol®	Diuretic / stimulate urine & salt loss	
Isradipine	Dynacirc®	Anti-hypertensive / high blood pressure	
Lapatinib	Tykerb®	Anti-cancer / breast cancer, metastatic	
Lapatinib	Tyverb®	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Levaquin®	Antibiotic / bacterial infection	
Lithium	Lithobid®	Anti-mania / bipolar disorder	
Lithium	Eskalith®	Anti-mania / bipolar disorder	
Mirtazapine	Remeron	Anti-depressant /	
Moexipril/HCTZ	Uniretic®	Anti-hypertensive / high blood pressure	
Nicardipine	Cardene®	Anti-hypertensive / high blood pressure	
Nilotinib	Tasigna®	Anti-cancer / Leukemia	
Octreotide	Sandostatin®	Endocrine / acromegaly, carcinoid diarrhoea	
Ofloxacin	Floxin®	Antibiotic / bacterial infection	
Olanzapine	Zyprexa®	Antipsychotic, atypical / Schizophrenia, bipolar	Combo c fluoxetine: Symbyax

Generic Name	Brand Name	Class/Clinical Use	Comments
Oxytocin	Pitocin®	Oxytocic / labour stimulation	
Paliperidone	Invega®	Antipsychotic, atypical / Schizophrenia	
Perflutren lipid microspheres	Definity®	Imaging contrast agent / Echocardiography	
Quetiapine	Seroquel®	Anti-psychotic / schizophrenia	
Ranolazine	Ranexa®	Anti-anginal / chronic angina	
Risperidone	Risperdal®	Anti-psychotic / schizophrenia	
Roxithromycin*	Rulide®	Antibiotic / bacterial infection	
Sertindole	Serdolect®	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sertindole	Serlect®	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sunitinib	Sutent®	Anti-cancer / RCC, GIST	
Tacrolimus	Prograf®	Immunosuppressant / Immune suppression	
Tamoxifen	Nolvadex®	Anti-cancer / breast cancer	
Telithromycin	Ketek®	Antibiotic / bacterial infection	
Tizanidine	Zanaflex®	Muscle relaxant /	
Vardenafil	Levitra®	phosphodiesterase inhibitor / vasodilator	

Generic Name	Brand Name	Class/Clinical Use	Comments
Venlafaxine	Effexor®	Anti-depressant / depression	
Voriconazole	VFend®	Anti-fungal / anti-fungal	
Ziprasidone	Geodon®	Anti-psychotic / schizophrenia	

D.3 Medications That Cause a Prolonged QT Interval and May Under Certain Circumstances Cause Torsades De Pointes

The following medications cause a prolonged QT interval and may under certain circumstances cause Torsades de pointes (Azcert.Org, 2013c).

Generic Name	Brand Name	Class/Clinical Use	Comments
Amisulpride	Solian® and others	Antipsychotic, atypical /	Risk of TdP with overdose
Amitriptyline	Elavil®	Tricyclic Antidepressant / depression	Risk of TdP with overdosage
Ciprofloxacin	Cipro®	Antibiotic / bacterial infection	Drug interaction risk - metabolic inhibitor
Clomipramine	Anafranil®	Tricyclic Antidepressant / depression	
Desipramine	Pertofrane®	Tricyclic Antidepressant / depression	Risk of TdP with overdosage
Diphenhydramine	Benadryl®	Antihistamine / Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages
Diphenhydramine	Nytol®	Antihistamine / Allergic rhinitis, insomnia	Risk of QT increase/TdP in overdosages

Generic Name	Brand Name	Class/Clinical Use	Comments
Doxepin	Sinequan®	Tricyclic Antidepressant / depression	
Fluconazole	Diflucan®	Anti-fungal / fungal infection	Drug interaction risk-metabolic inhibitor. Can also increase QT at high doses - 800 mg/day
Fluoxetine	Sarafem®	Anti-depressant / depression	
Fluoxetine	Prozac®	Anti-depressant / depression	
Galantamine	Reminyl®	Cholinesterase inhibitor / Dementia, Alzheimer's	
Imipramine	Norfranil®	Tricyclic Antidepressant / depression	TdP risk with excess dosage
Itraconazole	Sporanox®	Anti-fungal / fungal infection	Drug interaction risk - metabolic inhibitor
Ketoconazole	Nizoral®	Anti-fungal / fungal infection	Prolongs QT & Drug interaction risk - metabolic inhibitor.
Nortriptyline	Pamelor®	Tricyclic Antidepressant / depression	
Paroxetine	Paxil®	Anti-depressant / depression	
Protriptyline	Vivactil®	Tricyclic Antidepressant / depression	
Ritonavir	Norvir®	Protease inhibitor / HIV	
Sertraline	Zoloft®	Anti-depressant / depression	
Solifenacin	VESIcare®	muscarinic receptor antagonist / treatment of overactive bladder	

Generic Name	Brand Name	Class/Clinical Use	Comments
Trazodone	Desyrel®	Anti-depressant / Depression, insomnia	
Trimethoprim-Sulfa	Septra® or Bactrim®	Antibiotic / bacterial infection	
Trimipramine	Surmontil®	Tricyclic Antidepressant / depression	

The SSRIs have been highlighted in the above lists.

Appendix E Detailed Literature Search by Database

E.1 AMED / CINAHL/ Medline/ PsychInfo

(Limited to English Language; Human; Pregnancy; Infant; Newborn; Neonatal; birth- 1month; January 2005- April 2018)

	Search Terms	Number of Articles
1	Children OR neonate	47,810
2	Neonat* OR newborn	125,230
3	Baby	3,820
4	1 OR 2 OR 3	129,972
5	cardi* OR ECG OR EKG	2,021,824
6	QT OR electrocardio*	279,156
7	5 OR 6	2,120,330
8	4 AND 7	13,443
9	pregnan* OR antenatal*	1,173,834
10	8 AND 9	3,089
11	SSRI OR selective serotonin reuptake inhibitors	25,975
12	SRI	27,256
13	Citalopram OR escitalopram	12,332
14	Dapoxetine OR fluoxetine	25,686
15	Paroxetine	10,734
16	Sertraline	8,783
17	Indalpine OR fluvoxamine	4,926
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17	91,634
19	8 AND 18	31
20	Duplicates removed	27

This produced 27 articles that fitted the above criteria. These were reviewed and provided 2 relevant articles.

E.2 CLINICALTRIALS.GOV

	Search Words	Number of Articles
1	Neonate AND SSRI	5

Articles were reviewed, and 1 relevant paper was retained. However, this article was a listing for this study.

E.3 COCHRANE

	Search Words
1	Neonat*
2	Substance related disorders

This search produced 3 articles, but none were relevant.

E.4 DELPHIS

(Limited to full text; English; Human; 01/01/2005- 31/04/2018; remove duplicates)

	Search Terms	Number of Articles
1	Children OR neonate	2,685,190
2	Baby	98,434
3	Neonat* OR newborn	559,651
4	1 OR 2 OR 3	3,081,950
5	cardi* OR ECG OR EKG	8,631,636
6	QT OR electrocardio*	600,315
7	5 OR 6	8,824,331
8	4 AND 7	184,266
9	pregnan* OR antenatal*	2,849,816
10	8 AND 9	14,458

	Search Terms	Number of Articles
11	SSRI OR selective serotonin reuptake inhibitors	84,212
12	SRI	260,634
13	Citalopram OR escitalopram	39,248
14	Dapoxetine OR fluoxetine	85,029
15	paroxetine	34,131
16	sertraline	27,815
17	indalpine OR fluvoxamine	15,776
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17	472,944
19	10 AND 18	151

These were reviewed, and 5 relevant articles retained.

E.5 Embase/ OVID Medline/ Journals @OVID / Your Journals @OVIDfulltext including PsycArticles/ Ovid Medline Epub Ahead of Print, In Process and Other Non-Indexed Citations, Ovid Medline ® Daily, Ovid Medline and Versions ®

(Limited to 2005-current; Humans; English Language; Full Text; Ovid Full Text; Pharmacologic actions, Core Clinical Journals, Newborn Infant (birth to 1 month)).

	Search Words	Number of Articles
1	Child OR infant OR newborn OR neonat* OR baby	4,415,236
2	Cardi* OR electrocardio* OR QT interval OR QT prolongation	4,631,334
3	Pregnan* OR antenat*	2,046,045
4	Depression OR SSRI OR selective serotonin reuptake inhibitors OR citalopram OR dapoxetine OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR indalpine	192,937
5	1 AND 2 AND 3 AND 4	1,694

	Search Words	Number of Articles
6	Deduplicate	1,473
7	Add limitations	96

These articles were reviewed but not relevant.

E.6 EU CLINICAL TRIAL REGISTER

	Search Words	Number of Articles Obtained
1	SSRIs AND Pregnancy	21

These articles were reviewed but 0 were relevant.

E.7 IBSS

(Limited to 01/01/2005- 25/04/2018; English; articles; scholarly journals)

	Search Words	Number of Articles
1	Depression AND antenatal	0
2	Pregnancy AND SSRI	0
3	SSRI AND QT prolongation	0
4	Pregnan* OR antenat* AND depression OR SSRI AND child* OR infant OR newborn	0

This search produced 0 articles.

E.8 ISRCTN REGISTRY

(Limited to 2005-2018)

	Search Word	Number of Articles
1	SSRI	60
2	QT interval AND Mental and behavioural disorders	2
3	Pregnancy AND Depression AND Mental and behavioural disorders	143

This search produced 0 relevant articles

E.9 GOOGLE

	Search Words	Number of Articles
1	Neonate and QT and SSRI OR selective serotonin reuptake inhibitors OR SRI OR citalopram OR escitalopram OR dapoxetine OR fluoxetine OR paroxetine OR sertraline OR indalpine OR fluvoxamine	5

This search produced 4 relevant articles; a further article related to this study

E.10 MIDIRS

	Search Words	Number of Articles
1	Cardi* OR electrocardio* OR QT interval OR QT prolongation	0
2	Depression OR SSRI OR selective serotonin reuptake inhibitors OR citalopram OR dapoxetine OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR indalpine	0

This search produced 0 articles

E.11 NICE

(Limited to 2005-2018; Guidance; Systematic Reviews; Evidence Summaries; Primary Research; Medicines Current Awareness; Drugs and Technologies; 2005-2018)

	Search Words	Number of Articles
1	Antenatal depression	90

Articles were reviewed and produced 0 relevant articles.

E.12 OPEN GREY

	Search Words	Number of Articles
1	Neonate AND SSRIs AND QT	0
2	Neonate AND SSRIs	0
3	Neonate	62
4	English	41

No relevant articles were retained.

E.13 PROSPERO

	Search Words	Number of Articles
1	Depression AND pregnancy AND SSRI AND QT	0
2	Pregnancy AND Depression	294

These articles were reviewed and 0 retained.

E.14 SCOPUS

(Limited to 2005-2018; Articles; English)

	Search Words	Number of Articles
1	Children OR neonate OR Neonat* OR newborn OR Baby AND cardi* OR ECG OR EKG OR QT OR electrocardio* AND pregnan* OR antenatal* AND SSRI OR selective serotonin reuptake inhibitors OR SRI OR citalopram OR escitalopram OR dapoxetine OR fluoxetine OR paroxetine OR sertraline OR Indalpine OR fluvoxamine	57

These were reviewed, and 1 relevant article retained.

E.15 TRIP

(Limited to English/ primary research)

	Search Words	Number of Articles Obtained
1	Depression AND Pregnancy AND Treatment	40
2	2005-2017	36

These were reviewed, and 0 relevant articles retained.

E.16 WEB OF SCIENCE

(Limited to English; Article; 2005- 2018)

Search Words	Number of Articles
Child AND Depression AND Cardio*	468

There were no relevant articles, but one article had 2 relevant references which were retained.

E.17 WHO Clinical Trials

	Search words	Number of Articles Obtained
1	SSRIs AND pregnancy AND prolonged QT	0
2	Pregnancy AND prolonged QT	1
3	Pregnancy AND SSRIs	7

These were reviewed but none were relevant. One was this study.

E.18 ZETOC

	Search words	Number of Obtained
1	“antenatal depression”	769

These were reviewed but 0 relevant articles were retained.

Appendix F Retained Articles from the Literature Search Applied to a Critiquing Framework (Adapted from Critical Appraisal Skills Programme Check Lists (CASP, 2017); Critiquing Framework by Cluett And Bluff, 2006)

Authors/ Journal	Country	Research Type and Method (population studied- representative? how recruited? risk factors; exposure/ outcomes accurately measured; matched controls; bias minimised; blinding; follow up complete; time frame)	Methodological Aspects	Ethical Aspects	Main Findings (reliable; sufficient numbers; power calculation; association strength; p value)	Issues
Degiacomo J and Luedtke S (2016) Neonatal Toxicity from Escitalopram Use in Utero: A Case Report. *Journal of Pediatric Pharmacology and Therapeutics* 21(6): 522-526	Virginia, Texas USA Pharmacists Peer reviewed Aimed at those involved with paediatric and neonatal pharmacology	Case Report	Abstract covered all aspects but lacked signposting. Appropriate index terms. Justification for reporting case. Limited literature review to support statements	Nil stated	Term neonate with escitalopram affected behaviour soon after birth. Transferred to tertiary neonatal unit at 9 hrs old. Seizures-> medication. Prolonged QTc= 531msecs day two (ECG done because had a murmur and periods of bradycardia, when most of the time was tachycardic). Normal echocardiogram. Prolonged QT persisted until day seven and was gone by day 11. Believed to be due to toxicity (overdose) as other studies have not shown prolonged QTc with withdrawal.	Not a trial. Not an isolated QT prolongation-also withdrawal; respiratory distress;? sepsis; neurological signs

Appendix F

Dubnov G, Fogelman R and Merlob P (2005) Prolonged QT Interval in an Infant of a Fluoxetine Treated Mother *Archives of Disease in Childhood* 90 (9): 972-973	Israel Doctors Peer reviewed Aimed at medics and nurses in Neonatal; Cardiology; Paediatric care	Case Report	No abstract. No key words noted. Justification for reporting case. Limited literature review to support statements.	Nil stated	Term baby exposed to fluoxetine in pregnancy. Murmur noted on clinical exam. Normal routine blood urea + electrolytes. Routine ECG at 30 hours old- QTc was 540-580 msecs. Echocardiogram- NAD. Over next few days-> 380->360 msecs (normal). At two months old was 420 msecs (normal). Recommend routine ECG monitoring. Author previous experience of an infant with a prolonged QT -> Sudden infant death syndrome.	Not a trial Around time FDA statement expedited research on SSRIs.
Dubnov-Raz G, Juurlink D, Fogelman R, Merlob P, Ito S, Koren, G and Finkelstein Y (2008) Antenatal Use of Selective Serotonin Reuptake Inhibitors and QT Interval Prolongation in Newborns *Pediatrics* 122 (3): e7105	Israel/ Canada/ USA Doctors Peer reviewed Aimed at paediatric / neonatal staff. American Journal	Case-Controlled study. Prospective data collection- standard care. Retrospective review of notes/ ECGs for 2000-2005 52 in both groups Neonates >/=35/40 gestation ECG mostly day one- two Cases had SSRI exposure Controls had heart murmur- but normal Echocardiogram – unexposed to SSRIs Both Brazett and Frederica's formulas used. All normal ECGs when reviewed (up till one year old)	Abstract covered all aspects to be covered. There was justification for the study. Appropriate key words used. Literature to support statements- not related to QT prolongation in neonates exposed to SSRIs. Randomly matched- sex/ gestation. Blinded review of ECGs by cardiologist	Approved by hospital research ethics board	>460 msecs= 5/52 prolonged QTc v 0/52 in control >440 msecs= 6/52 prolonged QTc v 1/52 control	Not stated how neonates in each group were randomly matched. Included late preterm infants Only retrospectively follow up of those with prolonged QTc. No OR/ CI Use of case notes- Confounders not adjusted for- e.g., depression Authors of previous article on antenatal SSRI exposure causing a prolonged QT in neonate. Paroxetine was most commonly used SSRI

Appendix G Parent Information Sheets

Parent Information Sheet (Case)

Title of Project:- Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?

Researcher: Marie Lindsay-Sutherland Ethics number: 8442

Please read this information carefully before deciding to take part in this study. If you are happy to participate you will be asked to sign a consent form.

Why am I receiving this leaflet?

We would like to invite you and your baby to take part in a research study. Before you decide you need to understand why the research is being done and what it will involve for you both. This leaflet will explain this. Please ask if there is anything that you do not understand or would like more information about.

Part 1

Why is this study being done?

SSRIs such as Sertraline, Citalopram, and Fluoxetine, are a group of antidepressants used in the treatment of mental health problems. Their use in pregnancy may increase the risk of your baby being born early, having heart problems or having withdrawal symptoms. There is very limited information available, but it is also thought that use of these antidepressants in pregnancy may affect a baby's heart beat, in a way which can cause adults to collapse.

This study is looking at whether these antidepressants, when taken in pregnancy, affect the way a baby's heart beats by doing an Electrocardiogram (ECG) at 48- 72 hours of age. We also want to compare this to babies whose mothers haven't taken these antidepressants in pregnancy. We hope to perform ECGs on about 120 babies in each group.

Why have I been invited?

Your maternity notes show that you have taken a SSRI antidepressant at some point in your pregnancy. We are asking all mothers who have done this to take part in the study.

Do I have to take part?

You do not have to take part. It is up to you to decide if you want to. This leaflet describes the study so you can make that decision. If you do decide to take part, you can withdraw at any time, without giving a reason. This will not affect the care you receive.

What will I have to do?

Taking part in this study will involve your baby having an ECG at 48 -72 hours of age. This test will be done when your baby is comfortable and settled. It involves placing sticky pads on your baby's chest, arms and legs which are then connected to the ECG machine. A print out of your baby's heart beat will be taken. This will take about 15 minutes. The sticky pads will then be removed. You will be told immediately if the ECG result looks normal at that time

by the Advanced Neonatal Nurse Practitioner or the person who has done the ECG. You can go home as planned if the result looks normal. A confirmed result will be sent to you in the post once the ECG has been checked by a senior member of the neonatal team. The result of your baby's ECG will be noted on your discharge letter and their hospital electronic record so your GP is aware. If there are concerns, you will be asked to remain in hospital for any further investigations or monitoring that may be needed.

What should I expect if I decide to take part?

You will have about 36 hours to read this leaflet before we ask if you would like to take part in the study. If you are happy to do so, we will arrange a suitable time and place to do your baby's ECG. We will give you a chance to ask any questions before we do the ECG. We will then ask you to sign a consent form which states you are happy for yourself and your baby to take part. Also that you allow us to use your baby's ECG result and your details, both which will be unidentifiable, in the study report. The consent form will also give us permission to look at your baby's records at 6 months of age to check their health. We will finally ask you some questions about yourself, your pregnancy, and your medication.

Expenses and payments

No expenses or payments are offered.

What are the possible disadvantages and risks of taking part?

We do not believe there will be any harm to you or your baby from taking part in this study. However, we understand that discussing your mental health and the effects of your medication on your baby may be upsetting. We aim to support you with any worries you may have at this time. Extra support will be provided if the ECG result is not normal and further monitoring is needed.

The sticky ECG pads are used on the delicate skins of premature babies without any problems.

A normal ECG result at this time will not exclude future unrelated problems.

What are the possible benefits of taking part?

An ECG is not offered to everyone. It may find an unexpected problem, or confirm a normal heart pattern. The information from the study that you and your baby give, may help improve the services provided for other babies born to mothers who have taken these antidepressants in their pregnancy.

What happens when the research study stops?

We hope to be able to use the information provided by you and your baby to decide whether all babies of mothers who took these antidepressants in their pregnancies, should have an ECG after birth.

What if there is a problem?

Any concerns about the way you have been taken care off during the study or any possible harm to you or you baby will be addressed (see part 2).

Will my taking part in the study be kept confidential?

All information about you and your baby will be handled confidentially (see part 2). This will only change if the safety of your baby and yourself are at risk. You will be told if this is necessary.

This completes Part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before you make any decisions.

Part 2

What will happen if I don't want to carry on with this study?

You can withdraw from the study at any time without giving a reason.

What if there is a problem or I have a complaint?

If you have a question about any part of this study, you can speak to the researcher, Marie Lindsay-Sutherland, who will do her best to answer it.

If you continue to have a concern or a complaint about this study you can contact the Research
Governance Manager, at the Research Governance Office (Address: University of Southampton, Building 37, Highfield, Southampton, SO17 1BJ ; Tel: +44 (0)23 8059 5058; Email: rgoinfo@soton.ac.uk . If you remain unhappy and want to take it further, this office can provide you with details of the University of Southampton Complaints Procedure.

If you have a concern or a complaint about the care you received from X NHS Foundation Trust
Hospital, you should contact Matron X X on 01202 448217 (Neonatal Unit) or Head of Midwifery, X X on 01202 442190. If you wish to make an official complaint, you can do this through the NHS Complaints Procedure. The hospital can provide you with details on how to do this.

Will my taking part in the study be kept confidential?

All the information which is collected about you and your baby during the course of the study will be kept strictly confidential unless it affects either your own or your baby's safety. It will be coded so that neither of you can be identified. All documents will be kept in a locked filing cabinet in a secure office. Identifying data such as your name and hospital number, will be kept with matching codes in a separate locked cabinet. All original data will be kept for 21 years as required by NHS policy. All anonymous data will be stored in a password protected computer.

What will happen to the information I give?

The results of the heart beat pattern and the questionnaire will be used for analysis.

What will happen to the results of the research study?

- A thesis
- Presentations Papers for publication (links will be available through the hospital's newsletter, Grapevine).

Who is organizing and funding this research?

This work is self-funded and will be used as part of the researcher's Doctorate.

Who has reviewed the study?

This study has been reviewed by X NHS Foundation Trust Hospital Research and Development Office and the X X – X Research Ethics Committee to make sure that you and your baby's safety, rights and dignity are protected.

Further information and contact details of the researcher

Marie Lindsay-Sutherland (Doctoral Research Student)

Neonatal Unit, X Hospital NHS Foundation Trust

X, X

Telephone:- X 442330 (Neonatal Unit)

Email:- Marie.l.Sutherland@X.nhs.uk

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Consultant Neonatologist / Clinical Lead, University Hospital Southampton NHS Foundation Trust

(023) 8079 6001 (NICU)

mike.hall@uhs.nhs.uk

If you have any concerns or need independent advice, you can contact the Patient Advise and Liaison Service (PALS) by calling X 448499 or by visiting the PALS Health Information Centre on X Rd near the hospital's main car park. Alternatively you can email them at PALS@X.nhs.uk If you decide to participate you will be asked to sign a consent form and given a copy of the consent form to keep for your records.

Thank you for taking the time to read this leaflet

Parent Information Sheet (Control)

Title of Project: Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?

Researcher: Marie Lindsay-Sutherland Ethics number: 8442

Please read this information carefully before deciding to take part in this study. If you are happy to participate you will be asked to sign a consent form.

Why am I receiving this leaflet?

We would like to invite you and your baby to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you both. This leaflet will explain this. Please ask if there is anything that you do not understand or would like more information about.

Part 1

What is this study being done?

SSRIs such as Sertraline, Citalopram, and Fluoxetine, are a group of antidepressants used in the treatment of mental health problems. Their use in pregnancy may increase the risk of a baby being born early, having heart problems or having withdrawal symptoms. There is very limited information available, but it is also thought that use of these antidepressants in pregnancy may also affect a baby's heart beat, in a way which can cause adults to collapse.

This study is looking at whether these antidepressants, when taken in pregnancy, affect the way a baby's heart beats by doing an Electrocardiogram (ECG) at 48- 72 hours of age. We also want to compare this to babies whose mothers haven't taken these antidepressants in pregnancy. We hope to perform ECGs on about 120 babies in each group.

Why have I been invited?

Your maternity notes show that you have not taken a SSRI antidepressant at any point in your pregnancy. We are asking mothers who have not taken these antidepressants in pregnancy to take part in this study.

Do I have to take part?

You do not have to take part. It is up to you to decide if you want to. This leaflet describes the study so you can make your decision. If you do decide to take part, you can withdraw at any time, without giving a reason. This will not affect the care you receive.

What will I have to do?

Taking part in this study will involve your baby having an ECG between 48 – 72 hours of age. This test will be done when your baby is comfortable and settled. It involves placing

sticky pads on your baby's chest, arms and legs which are connected to leads from the ECG machine. A print out of your baby's heart beat will be taken. This will take about 15 minutes. The sticky pads will then be removed. You will be told immediately if the ECG result looks normal at that time by the Advanced Neonatal Nurse Practitioner or the person who has done the ECG. You can go home as planned if the result looks normal. A confirmed result will be sent to you in the post once the ECG has been checked by a senior member of the neonatal team. The result of your baby's ECG will be noted on your discharge letter and their hospital electronic record so your GP is aware. If there are concerns, you will be asked to remain in hospital for any further investigations or monitoring that may be needed.

What should I expect if I decide to take part?

You will have at least 24 hours to read this leaflet before we ask if you would like to take part in the study. If you are happy to do so, we will arrange a suitable time and place to do your baby's ECG. We will give you a chance to ask any questions before we do the ECG. We will then ask you to sign a consent form which states you are happy for yourself and your baby to take part. Also that you allow us to use your baby's ECG result and your details, both which will be unidentifiable, in the study report. The consent form will also give us permission to look at your baby's records at 6 months of age to check their health. We will finally ask you some questions about yourself, your pregnancy, and to confirm that you have not taken any SSRI antidepressants in pregnancy.

Expenses and payments

No expenses or payments are offered.

What are the possible disadvantages and risks of taking part?

We do not believe there will be any harm to you or your baby from taking part in this study. We aim to support you with any worries you may have at this time. Extra support will be provided if the ECG result is not normal and further monitoring is needed.

The sticky ECG pads are used on the delicate skins of premature babies without any problems.

A normal ECG result at this time will not exclude future unrelated problems.

What are the possible benefits of taking part?

An ECG is not offered to everyone. It may find an unexpected problem, or confirm a normal heart pattern. The information from the study that you and your baby give, may help improve the services provided for babies born to mothers who have taken SSRI antidepressants in their pregnancy.

What happens when the research study stops?

We hope to be able to use the information provided by you and your baby to decide whether all babies of mothers who took SSRI antidepressants in their pregnancies, should have an ECG after birth.

What if there is a problem?

Any complaint about the way you have been taken care off during the study or any possible harm to you or you baby will be addressed (see part 2).

Will my taking part in the study be kept confidential?

All information about you and your baby will be handled confidentially (see part 2). This will only change if the safety of your baby and yourself are at risk. You will be told if this is necessary.

This completes Part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before you make any decisions.

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Who has reviewed the study?

This study has been reviewed by X NHS Foundation Trust Hospital Research and Development Office and the X X– X Research Ethics Committee to make sure that you and your baby's safety, rights and dignity are protected.

Further information and contact details of the researcher

Marie Lindsay-Sutherland (Doctoral Research Student)

Neonatal Unit, X Hospital NHS Foundation Trust

X, X

Telephone:- X 442330 (Neonatal Unit)

Email:- Marie.l.Sutherland@X.nhs.uk

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Dr Michael Hall

Consultant Neonatologist / Clinical Lead, University Hospital Southampton NHS Foundation Trust

(023) 8079 6001 (NICU)

mike.hall@uhs.nhs.uk

If you have any concerns or need independent advice, you can contact the Patient Advise and Liaison Service (PALS) by calling X 448499 or by visiting the PALS Health Information Centre
on X Rd near the hospital's main car park. Alternatively you can email them at PALS@[redacted].nhs.uk

If you decide to participate you will be asked to sign a consent form and given a copy of the consent form to keep for your records.

Appendix H Consent Forms

Title of Project: Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?

Name of Researcher: Marie Lindsay-Sutherland

Study Ethics Number: 8442

Patient Coding Number for this study:-

CONSENT FORM For Case Group (Version 6)

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 25/11/2015 (version 7) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation and that of my baby is voluntary and that we are free to withdraw at any time without giving any reason, without our medical care or legal rights being affected. ☐

3. I understand that relevant sections of my and my baby's medical notes, and data collected during the study, may be looked at by individuals from the University of Southampton, from regulatory authorities, or from X NHS Foundation Trust Hospital, where it is relevant to our taking part in this research. I give permission for these individuals to have access to our records. ☐

4. I agree to my baby's medical records/ electronic patient record being accessed to establish follow up given if there is an initial abnormal ECG, and to ascertain his/her wellbeing. ☐

5. I agree to taking part in the above study. ☐

6. I agree to my General Practitioner (GP) being advised of my participation in the study and the result of my baby's ECG. ☐

Data Protection

I understand that information collected about me during my participation in this study will be stored on a password protected computer and in a locked environment, and that this information will only be used for the purpose of this study. All files containing any personal data will be coded, and links to this primary data stored separately in a secure environment.

Please tick if required

I would like to be advised of the study results :- by post ……..

(your latest address will be obtained from electronic hospital records)

Or by email (fill in email address)…….....

Patient Coding Number for this study:-

Name of Participant	Date	Signature
Hospital Number	Date of Birth	
Name of Person taking consent	Date	Signature
Designation		
Baby's Date of Birth	Baby's Hospital Number	

Title of Project: Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?

Name of Researcher: Marie Lindsay-Sutherland

Study Ethics Number: 8442

Patient Coding Number for this study:-

CONSENT FORM For Control Group (Version 6)

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 25/11/2015 (version 7) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation and that of my baby is voluntary and that we are free to withdraw at any time without giving any reason, without our medical care or legal rights being affected. ☐

3. I understand that relevant sections of my and my baby's medical notes, and data collected during the study, may be looked at by individuals from the University of Southampton, from regulatory authorities, or from X NHS Foundation Trust Hospital, where it is relevant to our taking part in this research. I give permission for these individuals to have access to our records. ☐

4. I agree to my baby's medical records/ electronic patient record being accessed to establish follow up given if there is an initial abnormal ECG, and to ascertain his/her wellbeing. ☐

5. I agree to taking part in the above study ☐

6. I agree to my General Practitioner (GP) being advised of my participation in the study and the result of my baby's ECG. ☐

Data Protection

I understand that information collected about me during my participation in this study will be stored on a password protected computer and in a locked environment, and that this information will only be used for the purpose of this study. All files containing any personal data will be coded, and links to this primary data stored separately in a secure environment.

Please tick if required

I would like to be advised of the study results :- by post ……..

(your latest address will be obtained from electronic hospital records)

Or by email (fill in email address)…….....

Patient Coding Number for this study:-

Name of Participant	Date	Signature
Hospital Number	Date of Birth	
Name of Person taking consent	Date	Signature
Designation		
Baby's Date of Birth	Baby's Hospital Number	

Appendix I Data Collection Sheets

Title of Project:- **Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?**

Researcher:- Marie Lindsay-Sutherland

Coding Number:-

Data collection sheet for mothers who have **used** SSRIs (**case** group) and have been assessed against the inclusion/ exclusion criteria (see ward study poster)

Staff to complete from medical records and directly from mother.

Remember to put maternal/ baby ID on the consent form only and staple forms together. Place in locked cabinet in the transitional care unit office till collected by Marie.

Medical History (e.g., Depression; cardiac abnormality (**exclude from study**) ; Diabetes; Epilepsy; Hypothyroidism; low magnesium levels; low potassium levels; abnormality at birth; prolonged QT syndrome (**exclude from study**))

……

Family Medical History (First degree relatives) (e.g., congenital heart conditions; prolonged QT syndrome (**exclude from study**); abnormalities at birth).

……
…

……

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……

……

…… ……

Which SSRI Antidepressant(s) are/ were used? Dosage(s)?

……

…… ……...

When was it started? (if in pregnancy state gestation at the time of commencement) (month / year) ……...

……

What gestation was it stopped / is it still continuing?

……

What other medications were taken at any point in pregnancy? (e.g., diuretics; other antidepressants (**exclude from study**); over the counter medications)

……
……

……
……

……

Any alcohol use in pregnancy? Yes/ No (circle answer)

If yes, units per week? …….

Does the woman smoke? Yes/ No (circle answer)

If yes, how many a day? .....
Does the partner smoke? Yes/ No (circle answer)

Has the woman used “recreational” drugs at any point in her pregnancy? Yes/ No (circle answer)

If yes, what “recreational” drugs were taken? And when? (**exclude from study** if cocaine and methadone use)

……..

……..

……...

Has the woman ever taken recreational drugs? Yes/ No (circle answer)

Were the antenatal scans normal? (fetal cardiac anomaly/ confirmed genetic abnormality such as Trisomy 21- **exclude from study**)

……

… …….

Baby’s gestation at birth……

Baby’s gender ……

Baby’s weight (kgs)……

Has the baby had any problems since birth? (give details if any problems)

……
……

……

Was the initial newborn exam normal, including cardiac assessment? (give details if any problems) (persisting heart murmur >48 hours of age- **exclude from study**)

……
……

……
……

……

Mode of feeding? ……...

How many hours old is the baby at the time of the ECG? ……
……....

*The following is to be completed by the **neonatal team** after the ECG has been undertaken and assessed.*

QT Interval (milliseconds) stated on ECG

……

Confirmed QT Interval (milliseconds)

……..

Follow up required ……..

……....

……

Timeframe for follow up……...

Title of Project:- **Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?**

Researcher:- Marie Lindsay-Sutherland

Coding Number:-

Data collection sheet for mothers who have **NOT used** SSRIs (**control** group) and have been assessed against the inclusion/ exclusion criteria (see ward study poster)

Staff to complete from medical records and directly from mother.

Remember to put maternal/ baby ID on the consent form only and staple forms together. Place in locked cabinet in the transitional care unit office till collected by Marie.

Medical History (e.g., Depression; cardiac abnormality (**exclude from study**); Diabetes; Epilepsy; Hypothyroidism; low magnesium levels; low potassium levels; abnormality at birth; prolonged QT syndrome (**exclude from study)**)

……..…
…
……..
……..
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……..…
…

APPENDIX I

Family Medical

History (First degree relatives) (e.g., congenital heart conditions; prolonged QT syndrome (**exclude from study)**; abnormalities at birth)

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…

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…

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…

……
…… ……

What other medications were taken at any point in pregnancy? (e.g.,

diuretics; antidepressants (**exclude from study**); over the counter

medications)

……
……

……
……

……

Any alcohol use in pregnancy? Yes/ No (circle answer)

If yes, units per week? …….

Does the woman smoke? Yes/ No (circle answer)

If yes, how many a day? .....

Does the partner smoke? Yes/ No (circle answer)

Has the woman used “recreational” drugs at any point in her pregnancy? Yes/ No (circle answer)

If yes, what “recreational” drugs were taken? And when? (**exclude from study** if cocaine and methadone use)

……..

……..

Has the woman ever taken recreational drugs? Yes/ No (circle answer)

Were the antenatal scans normal? (fetal cardiac anomaly/ confirmed genetic abnormality such as Trisomy 21- **exclude from study**)

……

… ……

Baby's gender …….

Baby's weight (kgs) ……

Baby's gestation at birth …….....

Has the baby had any problems since birth? (give details if any problems)

……
……

……

Was the initial newborn exam normal, including cardiac assessment? (give details if

any problems) (persisting heart murmur >48 hours of age- **exclude from study**)

……
……

……
……

……

Why was the baby started on antibiotics?

……..
…
……
……

……

Blood culture negative at 48 hours ? Yes / No (circle answer) (**exclude from study** if no)

Mode of feeding? ……...

How many hours old is the baby at the time of the ECG? ……...

……

*The following is to be completed by the **neonatal team** after the ECG has been undertaken and assessed.*

QT Interval (milliseconds) stated on ECG

……..

QT Interval (milliseconds) on confirmation by neonatal staff

……...

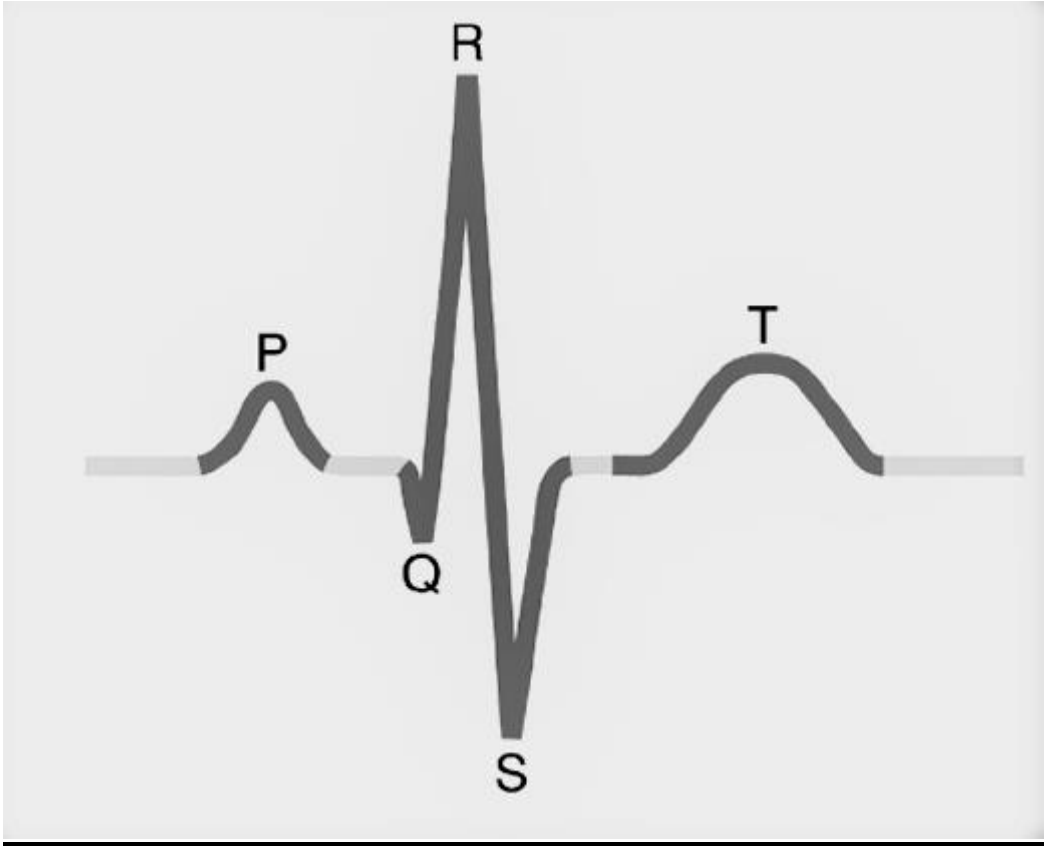
Follow up required ……..

……

……

Timeframe for follow up……...

Appendix J How to Read the ECG of a Day 2 Neonate



The ECG has a grid with thick lines 5 mm apart (= 0,20 second) and thin lines 1 mm (0,04 second). ECG speed= 25mm/ second. Voltage= 10mm

J.1 Check the Rhythm……

P wave must always precede QRS; regular; rate= 91-159bpm; check p wave height in **lead II** is 2.8mm (2.8 small squares) maximum; and P wave is positive in lead II.

J.2 Check the Rate……. (normal rate= 91- 159bpm) (ECG Pedia.org, 2011)

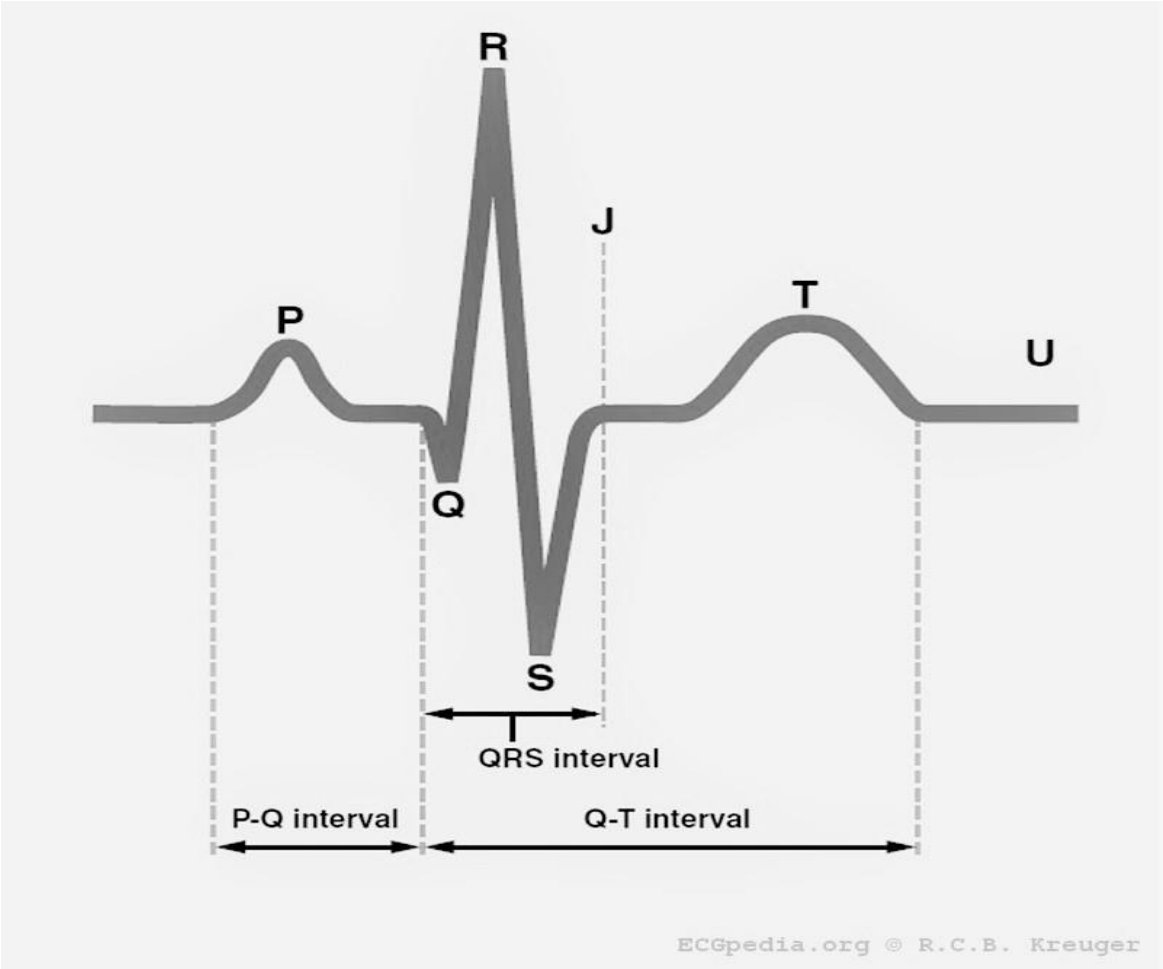
Use a calculator below

Count the small (1mm) squares between two QRS complexes. The ECG paper runs at 25 mm/sec through the ECG printer; therefore:

$$\text{Heart rate (beats/min)} = \frac{(25\ \text{mm/sec} \times 60\ \text{sec/min})}{\text{number of squares}} = \frac{1500}{\text{number of squares}}$$

(This method works well if >100 beats/minute)

J.3 Check Conduction…. (ECG Pedia.org, 2013b)



J.4 PR Interval

Start of P to R wave in **lead II**. 0.08- 0.14 secs (80-140 msecs) (2 small squares- 3.5 small squares)

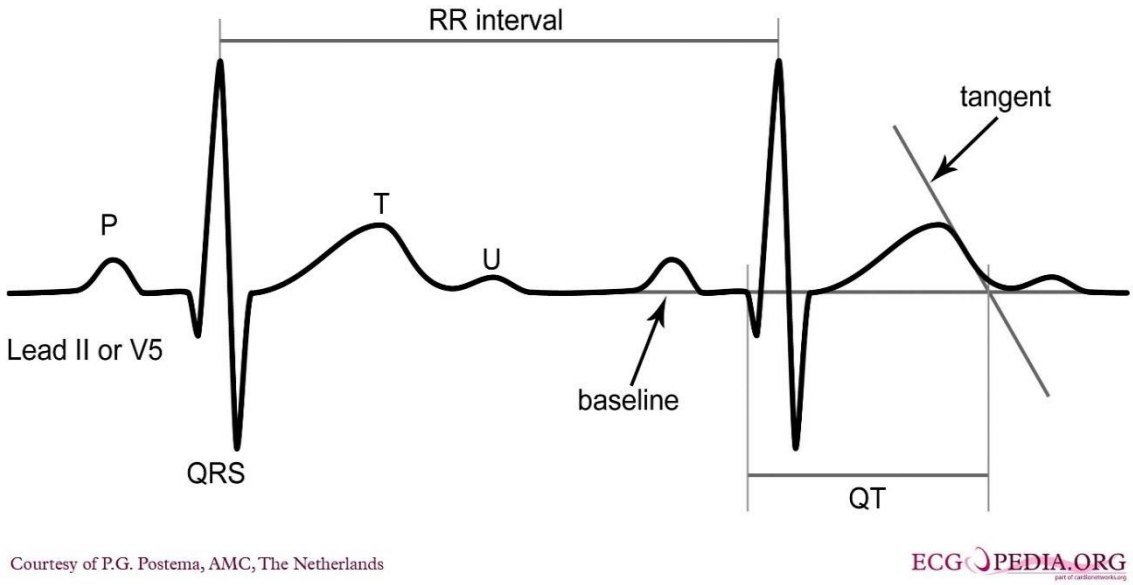
J.5 QRS Interval

Read in **V5**. Start of Q to end of S. 0.02 – 0.07 secs (20- 70 msecs) (0.5- 1.75 small squares)

(**RBBB**: if consistent morphology and if QRS width >90ms in children < 4 years

LBBB: if consistent morphology and QRS width >90ms in children < 4 years)

J.6 QT Interval



1. Use lead II
2. Draw a line through the baseline (preferably the PR segment)
3. Draw a tangent against the steepest part of the end of the T wave. If the T wave has two positive deflections, the taller deflection should be chosen. If the T wave is biphasic, the end of the taller deflection should be chosen.
4. The QT interval starts at the beginning of the QRS interval and ends where the tangent and baseline cross.

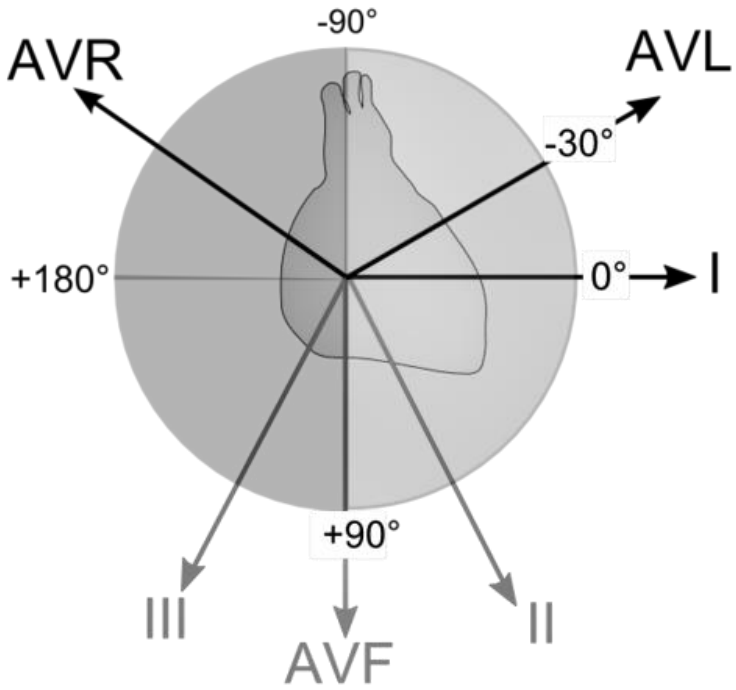
5. If the QRS duration exceeds 120ms the amount surpassing 120ms should be deducted from the QT interval (i.e. QT=QT-(QRS width-120ms)).
6. Calculate the QTc – normal value no greater than 440msecs (0.44secs)

http://en.ecgpedia.org/wiki/QTc_Calculator

J.7 Check the Axis…. (ECG Pedia. Org, 2010b)

Use leads I and III

QRS deflections in I and make that the X axis at 0 degrees (right = positive). You then add up all the QRS deflections in III and make that the Y axis at 90 degrees (down = positive). You then draw the resultant vector and see what angle its pointing to.



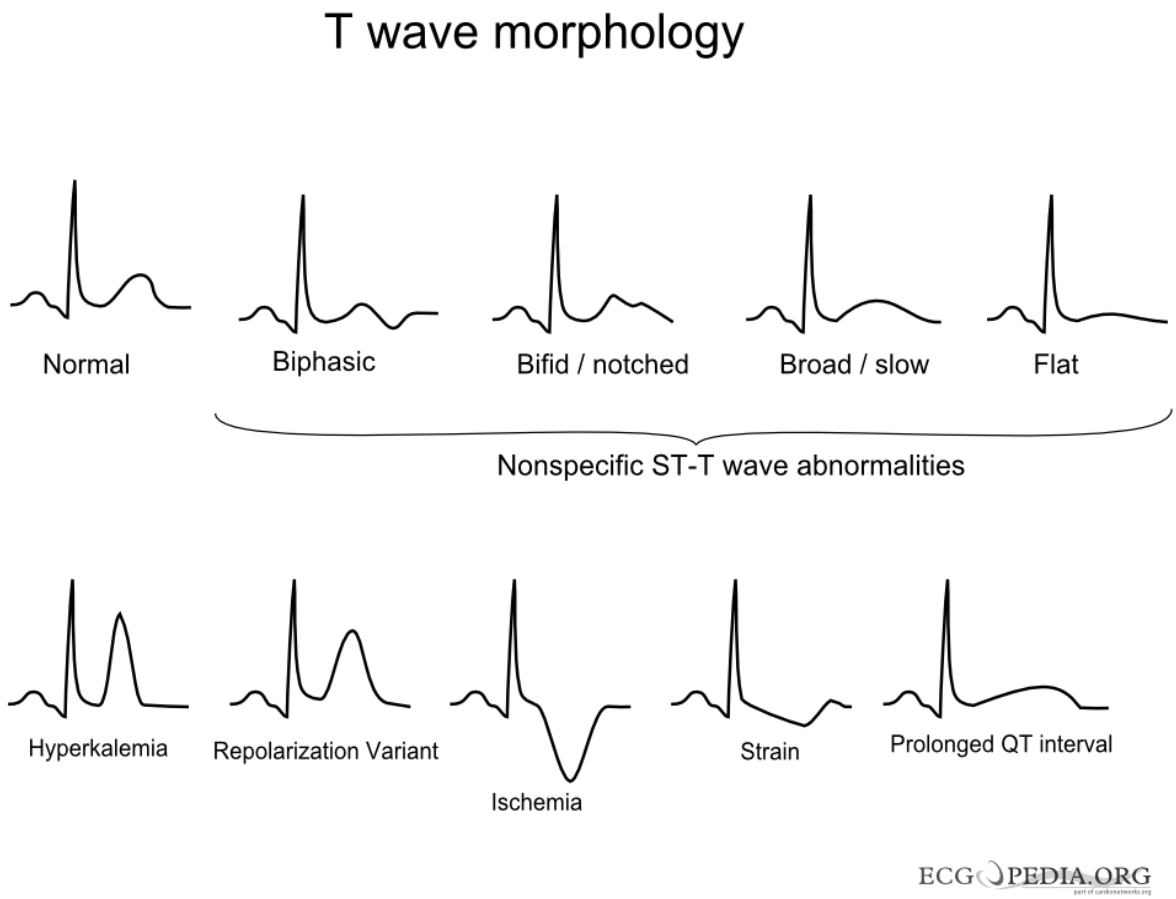
J.8 Normal Values (ECG Pedia. Org, 2010b)

Age group	Heart rate	Frontal plane QRS axis	P wave amp II	P-R invl II	QRS dur V_5	Q III	Q V_6	R V_1	S V_1	R/S V_1	R V_6	S V_6	R/S V_6	S V_1 + R V_6	R + S V_4
1-3 days	91-159 bpm	+64 to +197 degrees	2.8 mm	0.08-0.14 secs	0.02-0.07 secs	5.2 mm	2.1 mm	5-27 mm	0-21 mm	6	0-12 mm	0-9.5 mm	11	29 mm	52 mm

Msecs= secs x1000

J.9 Check T wave Morphology (ECG Pedia. Org, 2013c)

Look for ST elevation- abnormal



J.10 Distinguishing Tachyarrhythmias in Infants (ECG Pedia. Org, 2010b)

	Sinus tachycardia	**SVT**	**Atrial flutter**	**VT**
History	Sepsis, fever, hypovolaemia, etc.	Usually otherwise normal	Most have a normal heart	Many with abnormal heart
Rate	Almost always <230 b/min	Most often 260–300 b/min	Atrial 300–500 b/min. Vent. 1:1 to 4:1 conduction	200–500 b/min
R-R interval variation	Over several seconds may get faster and slower	After first 10–20 beats,	May have variable block (1:1, 2:1, 3:1) giving different	Slight variation over several beats

		extremely regular	ventricular rates	
P wave axis	Same as sinus almost always visible P waves	60% visible P waves, P waves *do not* look like sinus P waves	Flutter waves (best seen in LII, LIII, aVF, V_1)	May have sinus P waves continuing unrelated to VT (AV dissociation), retrograde P waves, or no visible P waves
QRS	Almost always same as slower sinus rhythm	After first 10–20 beats, almost always same as sinus	Usually same as sinus, may have occasional beats different from sinus	Different from sinus (*not* necessarily 'wide')

Appendix K Management of Prolonged QT Interval in Neonates

If this document is printed – please check in the Policies, Procedures and Guidelines section of the intranet to ensure this is the most up to date version

A) SUMMARY POINTS
This guideline has been constructed to ensure all staff are aware of their roles and responsibilities and the treatment required when a baby has a prolonged QT interval
A prolonged QT interval can lead to sudden death
A prolonged QT interval can be genetic or caused by drug exposure; electrolyte imbalance; auto-immune disorders. It is important that the pathology is determined and investigated appropriately.
The QT interval value will dictate the management of the neonate
B) ASSOCIATED DOCUMENTS
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Cifuentes J, Prieto F and Mendez L (2011) Simulation of a Neonatal Monitor for Medical Training Purposes. Available at: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S1794-12372011000200002 [Accessed 24/01/16]
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The Sudden Arrhythmia Death Syndromes (SADS) Foundation (2010) The Long QT Syndrome.

A guide for patients and health care providers. http://www.sads.org/sads/media/sads-materials---brochures/long-qt--3-2011.pdf [Accessed 13/01/16]

C) DOCUMENT DETAILS	
Author:	Marie Lindsay-Sutherland
Job title:	Lead ANNP
Directorate:	Child Health
Version no:	2
Target audience:	Neonatal Consultants; ANNPs; Midwives; Neonatal staff
Approving committee / group:	Neonatal Guideline Committee
Chairperson:	Dr X
Review Date:	Jan 2019

CONTENT **PAGE No.**

K.1 Introduction

This guideline applies to all neonatal health care professionals who are employed by X Hospital NHS Foundation Trust, including temporary, bank or agency staff.

This guideline is necessary for the management of babies who have been found to have a prolonged QT interval on Electrocardiogram (ECG).

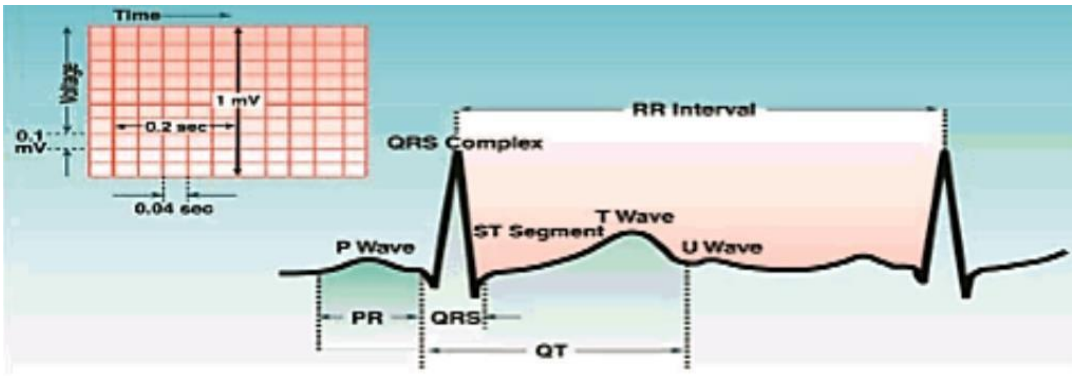
K.2 Purpose

This guideline has been constructed to provide guidance on the management of babies who have been found to have a prolonged QT interval.

This guideline identifies the principles of recognition, assessment, immediate treatment, monitoring and subsequent management.

K.3 Definitions

- QT interval- interval between beginning of QRS complex and end of T wave. See below diagram (Arrhythmia Alliance, 2008).



- How measured- Read in leads II, V5 and V6. Longest value used.

- Prolonged QT = > 440msecs (2 standard deviation from the mean).

- QTc- The QT interval changes with the heart rate so is corrected (QTc) by using the Bazett's Formula.

Bazett's formula= $\frac{\text{QT interval in seconds}}{\sqrt{\text{RR interval in seconds.}}}$

In order to avoid calculations, the table below was generated for ease (Schwartz et al, 2002).

- Causes of prolonged QT are electrolyte imbalance; drug exposure; being born to a mother with autoimmune diseases and positive anti- Ro and anti La antibodies; and congenital long QT syndrome (LQTS).

QTc (for heart rates between 81 and 176 beats.min^{-1})*

R-R interval

mm		8.50	8.75	9.00	9.25	9.50	9.75	10.00	10.25	10.50	10.75	11.00	11.25	11.50	11.75	12.00	12.25	12.50	12.75	13.00	13.25	13.50	13.75	14.00	14.25	14.50	14.75	15.00	15.25	15.50	15.75	16.00	16.25	16.50	16.75	17.00	17.25	17.50	17.75	18.00	18.25	18.50		mm
	msec	340	350	360	370	380	390	400	410	420	430	440	450	460	470	480	490	500	510	520	530	540	550	560	570	580	590	600	610	620	630	640	650	660	670	680	690	700	710	720	730	740	msec	
.00	240	412	406	400	395	389	384	379	375	370	366	362	358	354	350	346	343	339	336	333	330	327	324	321	318	315																	240	6.00
.25	250	429	423	417	411	406	400	395	390	386	381	377	373	369	365	361	357	354	350	347	343	340	337	334	331	328	325	323	320	318	315												250	6.25
.50	260	446	439	433	427	422	416	411	406	401	396	392	388	383	379	375	371	368	364	361	357	354	351	347	344	341	338	336	333	330	328	325	322	320	318	315							260	6.50
.75	270	463	456	450	444	438	432	427	422	417	412	407	402	398	394	390	386	382	378	374	371	367	364	361	358	355	352	349	346	343	340	338	335	332	330	327	325	323	320	318	316		270	6.75
.00	280	480	473	467	460	454	448	443	437	432	427	422	417	413	408	404	400	396	392	388	385	381	378	374	371	368	365	361	359	356	353	350	347	345	342	340	337	335	332	330	328	325	280	7.00
.25	290	497	490	483	477	470	464	459	453	447	442	437	432	428	423	419	414	410	406	402	398	395	391	388	384	381	378	374	371	368	365	363	360	357	354	352	349	347	344	342	339	337	290	7.25
.50	300	514	507	500	493	487	480	474	469	463	457	452	447	442	438	433	429	424	420	416	412	408	405	401	397	394	391	387	384	381	378	375	372	369	367	364	361	359	356	354	351	349	300	7.50
.75	310	532	524	517	510	503	496	490	484	478	473	467	462	457	452	447	443	438	434	430	426	422	418	414	411	407	404	400	397	394	391	388	385	382	379	376	373	371	368	365	363	360	310	7.75
.00	320	549	541	533	526	519	512	506	500	494	488	482	477	472	467	462	457	453	448	444	440	435	431	428	424	420	417	413	410	406	403	400	397	394	391	388	385	382	380	377	375	372	320	8.00
.25	330	566	558	550	543	535	528	522	515	509	503	497	492	487	481	476	471	467	462	458	453	449	445	441	437	433	430	426	423	419	416	413	409	406	403	400	397	394	392	389	386	384	330	8.25
.50	340		575	567	559	552	544	538	531	525	518	513	507	501	496	491	486	481	476	471	467	463	458	454	450	446	443	439	435	432	428	425	422	419	415	412	409	406	404	401	398	395	340	8.50
.75	350			583	575	568	560	553	547	540	534	528	522	516	511	505	500	495	490	485	481	476	472	468	464	460	456	452	448	445	441	438	434	431	428	424	421	418	415	412	410	407	350	8.75
.00	360				592	584	576	569	562	555	549	543	537	531	525	520	514	509	504	499	494	490	485	481	477	473	469	465	461	457	454	450	447	443	440	437	433	430	427	424	421	418	360	9.00
.25	370					600	592	585	578	571	564	558	552	546	540	534	529	523	518	513	508	504	499	494	490	486	482	478	474	470	466	463	459	455	452	449	445	442	439	436	433	430	370	9.25
.50	380						608	601	593	586	579	573	566	560	554	548	543	537	532	527	522	517	512	508	503	499	495	491	487	483	479	475	471	468	464	461	457	454	451	448	445	442	380	9.50
.75	390							617	609	602	595	588	581	575	569	563	557	552	546	541	536	531	526	521	517	512	508	503	499	495	491	488	484	480	476	473	470	466	463	460	456	453	390	9.75
.00	400								625	617	610	603	596	590	583	577	571	566	560	555	549	544	539	535	530	525	521	516	512	508	504	500	496	492	489	485	482	478	475	471	468	465	400	10.00
.25	410									633	625	618	611	605	598	592	586	580	574	569	563	558	553	548	543	538	534	529	525	521	517	513	509	505	501	497	494	490	487	483	480	477	410	10.25
.50	420										640	633	626	619	613	606	600	594	588	582	577	572	566	561	556	551	547	542	538	533	529	525	521	517	513	509	506	502	498	495	492	488	420	10.50
.75	430											648	641	634	627	621	614	608	602	596	591	585	580	575	570	565	560	555	551	546	542	538	533	529	525	521	518	514	510	507	503	500	430	10.75
.00	440												656	649	642	635	629	622	616	610	604	599	593	588	583	578	573	568	563	559	554	550	546	542	538	534	530	526	522	519	515	511	440	11.00
.25	450													663	656	650	643	636	630	624	618	612	607	601	596	591	586	581	576	572	567	563	558	554	550	546	542	538	534	530	527	523	450	11.25
.50	460														671	664	657	651	644	638	632	626	620	615	609	604	599	594	589	584	580	575	571	566	562	558	554	550	546	542	538	535	460	11.50
.75	470															678	671	665	658	652	646	640	634	628	623	617	612	607	602	597	592	588	583	579	574	570	566	562	558	554	550	546	470	11.75
.00	480																686	679	672	666	659	653	647	641	636	630	625	620	615	610	605	600	595	591	586	582	578	574	570	566	562	558	480	12.00
.25	490																	693	686	680	673	667	661	655	649	643	638	633	627	622	617	613	608	603	599	594	590	586	582	577	574	570	490	12.25
.50	500																		700	693	687	680	674	668	662	657	651	645	640	635	630	625	620	615	611	606	602	598	593	589	585	581	500	12.50
.75	510																			707	701	694	688	682	676	670	664	658	653	648	643	638	633	628	623	618	614	610	605	601	597	593	510	12.75
.00	520																				714	708	701	695	689	683	677	671	666	660	655	650	645	640	635	631	626	622	617	613	609	604	520	13.00
	msec	340	350	360	370	380	390	400	410	420	430	440	450	460	470	480	490	500	510	520	530	540	550	560	570	580	590	600	610	620	630	640	650	660	670	680	690	700	710	720	730	740	msec	
mm		8.50	8.75	9.00	9.25	9.50	9.75	10.00	10.25	10.50	10.75	11.00	11.25	11.50	11.75	12.00	12.25	12.50	12.75	13.00	13.25	13.50	13.75	14.00	14.25	14.50	14.75	15.00	15.25	15.50	15.75	16.00	16.25	16.50	16.75	17.00	17.25	17.50	17.75	18.00	18.25	18.50		mm

QT interval

R-R interval

Paper speed: 25 mm.s^{-1} ; Bazett's formula

e 1 Chart for calculation of QTc. QTc, according to the Bazett's formula is obtained by matching QT and RR interval in millimetres, given the paper speed mm . s^{-1}. Corresponding values of RR interval and uncorrected QT interval are also indicated.

K.4 Guideline

- **If QT interval is prolonged, then: -**

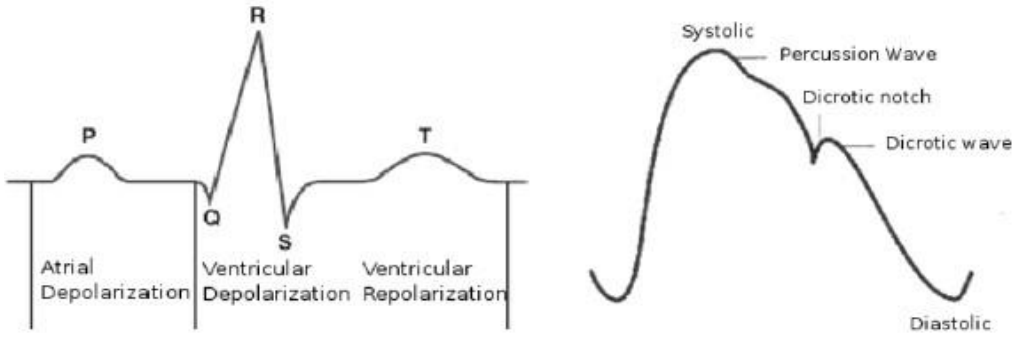
➢ Exclude other causes of prolongation as above

➢ Ascertain Urea and Electrolytes (including Calcium and Magnesium) are within normal limits

➢ Review family history for sudden collapse / death / LQTS

➢ If QTc is ≥ 470 msecs on first ECG then discuss with Southampton Paediatric Cardiology Team for further management plan

➢ Check ECG for notches on T wave as suggestive of LQTS. See the below diagram (Cifuentes et al, 2011)



(a) Depolarization and re-polarization of the heart. Adapted from Jones (2005)

(b) Characteristics of the pulse signal. Taken from Clara *et al.* (2005)

Figure 1. The ECG and the pulse signals

➢ Check ECG for mild bradycardia as can be suggestive of LQTS

➢ If QTc is prolonged on first ECG, a 2nd ECG is required: -

QTc (msecs) on first ECG	Timing of next ECG	Discharge from Hospital
>440 < 470	Within 1-2 weeks	Yes, with information leaflet (see appendix 1)
≥ 470 <500	Same day/ next day	No. Discuss with Southampton Paediatric Cardiology Team
≥500	Same day	No. Discuss with Southampton Paediatric Cardiology Team

NB- QTc close to 600 msecs is very high risk and highly suggestive of LQTS

General Guidance for Parents Once Southampton Paediatric Cardiology Team Input Sought

Babies with a very prolonged QTC are more likely to develop an arrhythmia if exposed to: -

- Sudden noises such as alarm clocks/ slamming hospital bins, especially when asleep
- Intense emotions such as pain or upset

Therefore, parents of these neonates should aim for to provide a quiet and calm environment for their baby.

- Parents should be given a leaflet on prolonged QT interval (see Appendix 1).

- Parents should be supported during hospital stay and aware of follow up appointments at discharge.

- Consider resuscitation training if indicated/ requested.

K.5 Roles and Responsibilities

Nursing / Midwifery staff

The Nursing / Midwifery staff member has a duty and responsibility: -

- To support parents with care of neonate
- To provide a quiet environment for the family to be cared for in.
- To provide resuscitation training as indicated/ requested.

NICU medical team

The NICU Consultants / Dr /ANNP have a duty and responsibility: -

- To provide consistent plan of treatment.
- To support parents with care of neonate.
- To review family history thoroughly.
- To order ECG/ ECHO/ 24-hour tape as indicated after discussion with Southampton Paediatric Cardiology Team
- To order blood investigations as detailed above and as requested by the Southampton Paediatric Cardiology Team
- To interpret investigations appropriately
- To commence pharmacological therapy as detailed by the Southampton Paediatric Cardiology Team
- To provide follow up as indicated.

K.6 Training

All medical staff should be competent in the management of babies with prolonged QT interval

K.7 Appendix 1

Information Leaflet for Parents of Neonates with Prolonged QT Interval

Your baby had an Electrocardiogram (ECG) which shows that a portion of their heart beat (QT) took longer than normal to happen. When this lengthening happens, it may lead to an abnormal heart rhythm (Arrhythmia).

Several things can cause this lengthening of the QT. The way the heart beats naturally changes in the first 6 months of life. However, the baby's QT can be affected by medications taken by the mother during pregnancy; chemical imbalances in baby, possibly from dehydration; by certain conditions the mother has; and by a rare inherited disorder in the family.

The lengthening of the QT may resolve by itself with no treatment. However, your baby needs to be investigated further to rule out the more serious causes which do need medicine and lifestyle changes.

The neonatal team will take advice about your baby from a paediatric heart specialist. This heart specialist may request that your baby has regular ECGs; a heart scan (ECHO); and blood tests. Both parents and any other children may also need to have an ECG. The neonatal team will explain which investigations are planned. It is very important that you attend any follow up appointments.

Babies with a very prolonged QT are more likely to develop an abnormal heart rhythm if: -

- They are woken by sudden noises such as alarm clocks
- They get very upset
- They are in pain

You can help with this by providing a quiet, comfortable and calm environment for your baby.

Also, when you have skin to skin with your baby, take time to feel your baby's heartbeat, so that you may recognize when it is different.

If you are concerned about your baby's health, you should seek medical attention immediately.

Appendix L Clinical Trials Participation Statement from GCP for Inpatient Hospital Notes

Date:

Time:

Research Study Participation

Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with a Prolonged QT Interval in Term Neonates (37 Weeks Gestation or Greater)?

Having been given Patient Information Leaflet- Version 7- 25/11/15……., gave consent for herself and her baby to participate in the above study on ……. at ……. to …… As a result, a questionnaire was completed, and an ECG was performed on her baby.

The ECG result looks normal and they are discharged from the hospital with no follow up.

Appendix M Parent Letter for Result Confirmation

XXXXX Hospital NHS Foundation Trust

XXXXX Rd

XXXX

XXXX

XXXXXX

Dear

Thank you for your participation and that of your baby in the study being undertaken in the Maternity Unit at XXXX NHS Foundation Trust Hospital entitled "Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?"

Your baby's ECG has been manually checked and I can confirm that it is normal.

Best Wishes

Marie Lindsay-Sutherland

Principal Investigator/ Lead Advanced Neonatal Nurse Practitioner

Appendix N Standardised Communication with General Practitioner to be Entered (Cut and Paste) on the Medway Discharge System for Study Participants

(Insert name) consented to the participation of herself and her baby in a study being undertaken in the Maternity Unit at XXXX NHS Foundation Trust Hospital entitled “Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with a Prolonged QT Interval in Term Neonates (37 Weeks Gestation or Greater)?”

As a result, her baby received an ECG at 48-72 hours of age.

(*Delete the following as appropriate*)

- The ECG result looks normal and they are discharged from the hospital with no follow up. The ECG will be manually checked within 24 hours and the confirmed normal result will be added to the electronic patient record system. Postal confirmation will also be sent to the mother if she did not receive it before discharge.

- The ECG showed (insert abnormal result findings) and the baby will be followed up (insert follow up).

Appendix O Standardised Communication to be Entered on the Hospital Electronic Patient Record System for Study Participants

(Insert name) consented to the participation of herself and her baby in a study being undertaken in the Maternity Unit at XXXX NHS Foundation Trust Hospital entitled “Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with a Prolonged QT Interval in Term Neonates (37 Weeks Gestation or Greater)?”

As a result, her baby received an ECG at 48-72 hours of age.

(*Delete the following as appropriate*)

- The ECG result was checked by the Advanced Neonatal Nurse Practitioner Team/ Neonatal Consultants and is confirmed as normal.

- The ECG showed (insert abnormal result findings) and the baby will be followed up (insert follow up).

Appendix P Women and Neonates Considered for the Study

Gender	Study Group	Comments
M	Case	Fluoxetine. Normal QT (63)
M	Case	Venlafaxine
M	Case	Sertraline. Not available to recruit
M	Case	Sertraline. Not available to recruit
F	Case	Amitriptyline
F	Case	Sertraline. Premature
F	Case	Fluoxetine. Normal QT (62)
F	Case	Mirtazapine
F	Case	Fluoxetine. Cardiomyopathy in sibling
M	Case	Paroxetine. Declined
M	Case	Fluoxetine. Normal QT (58). Superior axis -> ECHO 1/52
M	Case	Sertraline. Normal QT (59)
M	Case	Normal QT (61) Unusual lead II-> repeat
F	Case	Venlafaxine
F	Case	Sertraline- Not available to recruit
F	Case	Venlafaxine
M	Case	Citalopram- Declined
M	Case	Premature
M	Case	Premature
M	Case	Venlafaxine-> Sertraline
F	Case	Premature
F	Case	Non-SSRI
F	Case	Home before 48 hours old

F	Case	Citalopram. Declined
F	Case	Fluoxetine. Declined
M	Case	Venlafaxine/ Amitriptyline/ Preterm
M	Case	Citalopram till 10/40- discharged <48 hours old
M	Case	Sertraline. Normal QT (53)
F	Case	Declined
F	Case	(50). Sertraline. Normal QT
F	Case	Non-SSRI
F	Case	Sertraline. Cardiomyopathy in Dad
F	Case	Sertraline. Normal QT (52)
M	Case	Sertraline. Normal QT (88)
F	Case	Sertraline. Not invited in time
F	Case	Fluoxetine. Declined
M	Case	Sertraline. Premature
F	Case	Sertraline. Not available to recruit.
M	Case	Recruited but withdrawn as baby withdrawing ++ (w)
M	Case	Not available to recruit
M	Case	Sertraline. Normal QT (39)
M	Case	Non-SSRI and Fluoxetine
M	Case	Sertraline. Fetal pericardial effusion
F	Case	Home @8 hours old
F	Case	Fluoxetine. Normal QT (41)
F	Case	Early Sertraline. Home @ 24 hours old
F	Case	Non-SSRI
F	Case	Sertraline. Normal QT (87)
M	Case	Citalopram + Alcohol + drugs. Bradycardia-> ECG- NAD
M	Case	Clonazepam. Non-SSRI

F	Case	Non-SSRI
M	Case	Sertraline. Premature
M	Case	Sertraline. Premature
F	Case	Sertraline. Discharged <48 hours old
M	Case	Not available to recruit
F	Case	Normal QT (34)
F	Case	Venlafaxine
F	Case	Not invited in time
F	Case	Not invited in time
F	Case	Citalopram. Not available to recruit
M	Case	Mirtazapine
M	Case	Cardiac hx in mum + dad
M	Case	Normal QT (36)
F	Case	Citalopram. Declined
F	Case	Fluoxetine. Not invited in time
M	Case	Sertraline. Normal QT (80)
M	Case	Citalopram. Normal QT (81)
M	Case	Sertraline. Normal QT (82)
F	Case	Sertraline. Normal QT (83)
M	Case	Sertraline -> Fluoxetine. Normal QT (84)
F	Case	Sertraline. Declined
F	Case	Sertraline. Raised Na2+. Anxious
F	Case	Sertraline + alcohol +++
F	Case	Fluoxetine. Normal QT (86)
F	Case	Non-SSRI antidepressant
M	Case	Not invited in time
F	Case	Discharged before 48 hours old
F	Case	Sertraline. Premature

F	Case	Normal QT (30)
F	Case	Self-discharge <48 hours old
M	Case	Venlafaxine
M	Case	Venlafaxine + Sertraline
M	Case	Sertraline. Normal QT (78)
F	Case	Venlafaxine
M	Case	Sertraline. Not available to recruit
M	Case	Normal QT (21)
M	Case	Normal QT (22)
M	Case	Normal QT (25)
M	Case	Sertraline- not invited
M	Case	Normal QT (19)
M	Case	Normal QT (18)
M	Case	Normal QT (20)
M	Case	Not invited in time
M	Case	ECG machine broken- withdrawn (w)
F	Case	Normal QT (24)
F	Case	Declined
F	Case	Paroxetine. Normal QT (28)
F	Case	Venlafaxine
M	Case	Citalopram. Not invited in time
F	Case	Quetiapine. Cardiac Hx-> ECHO
F	Case	Sertraline. Not available to consent.
F	Case	Lithium + Sertraline
M	Case	Citalopram + unwell baby. Not appropriate to recruit
M	Case	Fluoxetine. Premature
M	Case	Non-SSRI + Citalopram
M	Case	Not invited in time

M	Case	Not invited in time
M	Case	Not invited in time
M	Case	Declined
F	Case	Citalopram. Normal QT (16)
F	Case	Not invited in time
F	Case	Not invited in time
F	Case	Citalopram. Self-discharge <48 hours old
M	Case	Sertraline. 2 cardiac deaths in children-> ECG @ 24 hours-> Abnormal-> Cardiology
M	Case	Sertraline. Not invited in time
F	Case	Sertraline. Mum unstable mentally. Not appropriate to recruit
M	Case	Sertraline <26/40. Discharged <48 hours old.
M	Case	Sertraline. Premature
F	Case	Sertraline. Declined
F	Case	Fluoxetine. Normal QT (76)
M	Case	Normal QT (8)
M	Case	Normal QT (4)
M	Case	Declined
M	Case	Not available to recruit
M	Case	Citalopram- consented but ECG not working so withdrawn (w)
F	Case	Normal QT (5)
F	Case	Not available to recruit
F	Case	Normal QT (2)
F	Case	Not invited in time
F	Case	Self-discharge @24 hours
F	Case	Not appropriate to approach -asleep

M	Case	Sertraline. Normal QT (69)
F	Case	Paroxetine. Not invited in time
M	Case	Citalopram. Normal QT (70)
F	Case	Sertraline. Not invited in time
F	Case	Fluoxetine. Normal QT (71)
M	Case	Sertraline. Normal QT (72)
M	Case	Citalopram 21-28/40. Ectopics-> ECG Day 1- NAD. Home <48 hours old.
F	Case	Sertraline. Normal QT (68)
M	Case	Normal QT (1)
F	Case	Declined then -> sepsis
M	Case	Premature
F	Case	Sertraline. Normal QT (65)
F	Case	6/52 sertraline only. Not invited in time
F	Case	Sertraline + Quetiapine + language
F	Case	Citalopram. Not available to consent
F	Case	Sertraline <15/40-> citalopram @ 39/40. Not available to consent
M	Case	Sertraline. Declined
F	Case	Sertraline + Imipramine
F	Case	Fluoxetine + murmur
M	Case	Venlafaxine
M	Case	Sertraline. NICU. Unwell
F	Case	Sertraline + Quetiapine
M	Case + Control	Bipolar meds till 6/40 plus ? sepsis
F	Case + Control	Amitriptyline in early pregnancy + ? sepsis
F	Case + Control	Fluoxetine + Quetiapine. Premature
F	Case + Control	Sertraline + ? sepsis. Premature

M	Case + control	Sertraline + ? sepsis
M	Case + control	SSRI + ? sepsis
F	Case + Control	Sertraline + other antidepressants + ? sepsis. NICU
M	Case + control	Sertraline. Premature
F	Case + control	Sertraline + diazepam. ?sepsis
F	Case + control	Sertraline + diazepam. ?sepsis
F	Case + control	Venlafaxine in early pregnancy + ?sepsis
M	Case + Control	Dosulepin + ?sepsis
F	Case + Control	Sertraline + ?sepsis
F	Case + Control	Language. SSRI + ?sepsis
F	Case + Control	Imipramine + ?sepsis
F	Case + Control	NICU. Citalopram. 5/7 Abx
M	Case + Control	Venlafaxine + ?sepsis
M	Case + Control	Citalopram + ? sepsis
F	Case + Control	Venlafaxine + ? sepsis. NICU. Unwell
M	Case + Control	Fluoxetine and ?sepsis
M	Case + control	Sertraline + 5/7 Abx
M	Case + Control	Sertraline + ? sepsis-> cooled. NICU
F	Case + Control	Citalopram + ? sepsis
F	Case + Control	Citalopram + sepsis
F	Case +Control	Sertraline + Abx
M	Case +Control	Non-SSRI + 5/7 Abx
M	Control	Discharged <48 hours old
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx

M	Control	5/7 Abx
M	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Declined
F	Control	5/7 Abx
F	Control	Not available to recruit
F	Control	Not available to recruit
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature
M	Control	Not available to recruit
M	Control	Normal QT (57)
M	Control	Deranged U+Es-> Unwell
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Baby murmur. Family hx- cardiac death. Language issue
M	Control	<18 years old
M	Control	Extended Abx
M	Control	5/7 Abx
F	Control	Premature
F	Control	Premature
F	Control	NICU. Bile vomit-> unwell
F	Control	NICU. Not appropriate to invite
F	Control	NICU. Not appropriate to invite
M	Control	Normal QT (12)
F	Control	Declined
F	Control	Normal QT (56)
F	Control	5/7 Abx

F	Control	Declined
F	Control	5/7 Abx
F	Control	Normal QT (60) Poor quality ECG-> Repeat -normal
F	Control	NICU-bile. Inappropriate to invite
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	5/7 Abx
M	Control	Not available to consent
M	Control	5/7 Abx
M	Control	Normal QT (54)
M	Control	Declined
M	Control	5/7 Abx
F	Control	Home before 48 hours old
F	Control	5/7 Abx
F	Control	Normal QT (55)
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Extended Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature
M	Control	<18 years old
M	Control	Declined
M	Control	Normal QT (51)
M	Control	Not appropriate to invite- anxious/ dropped baby

M	Control	Premature
M	Control	Not available to recruit
M	Control	Mum in ITU- not appropriate to invite
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	Not available to recruit
F	Control	Normal QT (49)
F	Control	5/7 Abx
F	Control	Premature/ PROM-> NICU/ Abx
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	Premature
F	Control	Unwell- raised Na2+
F	Control	Premature
F	Control	Not invited in time
F	Control	Not invited in time
M	Control	Normal QT (44)
M	Control	Normal QT (48)
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Bile aspirates-> soton. Nicu
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx/ premature
M	Control	Not available to recruit
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature

M	Control	5/7 Abx
M	Control	Normal QT (43)
M	Control	5/7 Abx
M	Control	Declined
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Normal QT (42)
M	Control	5/7 Abx
M	Control	Normal QT (40)
F	Control	Normal QT (45)
F	Control	Normal QT (46)
F	Control	Normal QT (47)
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	Language problem
F	Control	Home before 48 hours old
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Declined
F	Control	5/7 Abx
M	Control	5/7 Abx. NICU
F	Control	Not available to consent
F	Control	Normal QT (38)
F	Control	5/7 Abx
M	Control	Not available to consent
F	Control	Not available to consent
M	Control	5/7 Abx
M	Control	5/7 Abx

F	Control	5/7 Abx
M	Control	5/7 Abx. NICU. Murmur-> ECHO
M	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Declined
M	Control	5/7 Abx
F	Control	Declined
M	Control	Not invited in time
M	Control	Not invited in time
F	Control	5/7 Abx
F	Control	Discharged <48 hours old
F	Control	Extended Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature. VSD
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature
F	Control	Not available to consent
M	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx

M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	Premature
M	Control	Language
M	Control	5/7 Abx
F	Control	Language
F	Control	Declined
F	Control	5/7 Abx
F	Control	Discharged <48 hours old
M	Control	Normal QT (35)
M	Control	Cardiac hx-mum
M	Control	Twin 2 sick. Not appropriate to invite
M	Control	Language
F	Control	Normal QT (37)
F	Control	5/7 Abx
F	Control	Family hx cardiac-> early ECG
M	Control	Declined
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Premature
F	Control	Normal QT (79)
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	7/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	NICU. 7/7 Abx. PPHN. Unwell
M	Control	Not invited in time

F	Control	Normal QT (85)
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	Late starter. Not invited in time.
M	Control	Declined
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
F	Control	NICU. Unwell
F	Control	7/7 Abx
F	Control	5/7 Abx
M	Control	Language
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	Premature
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Declined
F	Control	Premature
F	Control	ECG Day 1- bradycardia

F	Control	Declined
F	Control	Premature
M	Control	5/7 Abx
F	Control	5/7 Abx. Premature
M	Control	Declined
F	Control	Premature
F	Control	Normal QT (31)
M	Control	Normal QT (32)
F	Control	5/7 Abx
F	Control	Normal QT (33)
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	Discharged <48 hours old
F	Control	Declined
M	Control	Not available to recruit
F	Control	Premature
M	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Extended Abx
F	Control	5/7 Abx
M	Control	Unwell- Raised resps
M	Control	Not available to recruit
M	Control	5/7 Abx
M	Control	Normal QT (23)
M	Control	5/7 Abx
M	Control	5/7 Abx

M	Control	5/7 Abx
M	Control	Not invited
M	Control	Declined
M	Control	Declined
M	Control	5/7 Abx
M	Control	NICU. Bile. Unwell.
M	Control	Normal QT (29)
F	Control	Home before 48 hours old
F	Control	Normal QT (26)
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Declined
F	Control	Recruited but baby hiccups ++-> Mum distressed -> declined repeat-> withdrawn (w)
F	Control	Not available to recruit
F	Control	Normal QT (27)
F	Control	5/7 Abx
F	Control	Maternal cardiac hx. Raised Na2+. Unwell
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature
F	Control	Premature

M	Control	5/7 Abx
F	Control	Normal QT (77)
F	Control	Premature
F	Control	Premature
F	Control	Not invited in time
M	Control	Mum unwell- HDU- unable to consent
M	Control	Language problem
M	Control	5/7 Abx
M	Control	Normal QT (15)
M	Control	Not appropriate to invite
M	Control	Declined
M	Control	5/7 Abx
M	Control	Declined
M	Control	Normal QT (14)
M	Control	Normal QT (11)
M	Control	Extended Abx
M	Control	Extended Abx
M	Control	Abx
F	Control	Normal QT (17)
F	Control	Not available to recruit
F	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	Declined
F	Control	5/7 Abx
F	Control	Normal QT (9)
F	Control	Normal QT (10)
F	Control	Not invited in time
	Control	Normal QT (13)
M	Control	7/7 Abx

M	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	Raised Na2+. Unwell
M	Control	Raised Na2+. Unwell
M	Control	5/7 Abx
M	Control	Not available to recruit
M	Control	Normal QT (73)
F	Control	5/7 Abx
F	Control	Not available to recruit
F	Control	Normal QT (75)
F	Control	Normal QT (74)
F	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	Not available to recruit
F	Control	Not available to recruit
M	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	Wanting to take early discharge. Persuaded to stay. Not appropriate to invite.
F	Control	5/7 Abx
F	Control	Mentally unwell Mum. Not appropriate to recruit
F	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	Declined
M	Control	Normal QT (7)
M	Control	Not available to recruit
M	Control	Premature

M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Normal QT (3)
M	Control	5/7 Abx
F	Control	Normal QT (6)
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Raised Na2+. Unwell
M	Control	Extended Abx
F	Control	Raised Na2+. Unwell
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	14/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx

M	Control	Discharged <48 hours old
M	Control	Family hx of cardiac
M	Control	Not available to recruit
F	Control	Declined
M	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
F	Control	Not available to recruit
M	Control	Not available to recruit
F	Control	5/7 Abx
M	Control	Not available to recruit
M	Control	5/7 Abx
M	Control	Declined- feeding mgmt.- no further testing
F	Control	Language
F	Control	<18 years old
M	Control	5/7 Abx
M	Control	Normal QT (64)
M	Control	5/7 Abx
M	Control	Not available to recruit
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	5/7 Abx
F	Control	Premature
F	Control	5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Not invited in time
M	Control	5/7 Abx
M	Control	Extended Abx

F	Control	5/7 Abx. NICU fitting. Unwell
F	Control	5/7 Abx
F	Control	Not invited in time
M	Control	Not available to consent
F	Control	Normal QT (66)
M	Control	Normal QT (67)
M	Control	5/7 Abx
M	Control	NICU. 5/7 Abx
F	Control	5/7 Abx
M	Control	5/7 Abx
M	Control	Premature
F	Control	Premature
M	Control	5/7 Abx

Appendix Q Table for Logging All QT interval Values

Baby Number	**QTc** **(milliseconds)**
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	

Appendix R Combined Dara Collected from Participants in SSPS Format

merged data all case and control together.sav

	Study_group	Age	Ethnicity	Mental_Hea lh_history	other_med_history
1	1.00	27.00	1.00	1.00	2.00
2	1.00	32.00	1.00	1.00	1.00
3	1.00	39.00	1.00	2.00	6.00
4	1.00	28.00	1.00	1.00	5.00
5	1.00	37.00	1.00	1.00	5.00
6	1.00	32.00	1.00	3.00	5.00
7	1.00	40.00	2.00	2.00	4.00
8	1.00	30.00	1.00	2.00	4.00
9	1.00	25.00	1.00	1.00	4.00
10	1.00	25.00	1.00	1.00	1.00
11	1.00	28.00	1.00	2.00	6.00
12	1.00	34.00	1.00	1.00	5.00
13	1.00	38.00	1.00	2.00	1.00
14	1.00	28.00	1.00	2.00	3.00
15	1.00	36.00	1.00	2.00	6.00
16	1.00	28.00	1.00	1.00	1.00
17	1.00	34.00	1.00	2.00	1.00
18	1.00	35.00	1.00	1.00	5.00
19	1.00	26.00	1.00	1.00	1.00
20	1.00	36.00	1.00	1.00	5.00
21	1.00	44.00	1.00	2.00	5.00
22	1.00	22.00	1.00	2.00	3.00
23	1.00	34.00	1.00	1.00	11.00
24	1.00	27.00	1.00	2.00	3.00
25	1.00	33.00	1.00	2.00	1.00
26	1.00	35.00	1.00	2.00	1.00
27	1.00	34.00	2.00	1.00	2.00
28	1.00	30.00	1.00	1.00	8.00
29	1.00	34.00	1.00	1.00	1.00
30	1.00	43.00	1.00	2.00	6.00
31	1.00	25.00	1.00	1.00	6.00
32	1.00	24.00	1.00	1.00	10.00
33	1.00	29.00	1.00	1.00	2.00
34	1.00	43.00	1.00	2.00	2.00
35	1.00	37.00	1.00	1.00	11.00
36	1.00	35.00	1.00	2.00	6.00
37	1.00	28.00	1.00	1.00	8.00

7/17/18 6:15 PM 1/24

merged data all case and control together.sav

	Smoking	partner_smoker	Alcohol_in_pregnan
1	1.00	1.00	2.00
2	1.00	1.00	1.00
3	1.00	1.00	1.00
4	3.00	1.00	1.00
5	1.00	1.00	1.00
6	2.00	2.00	1.00
7	1.00	3.00	1.00
8	2.00	2.00	1.00
9	1.00	1.00	1.00
10	1.00	3.00	1.00
11	1.00	1.00	1.00
12	1.00	4.00	1.00
13	1.00	3.00	1.00
14	1.00	1.00	1.00
15	3.00	1.00	1.00
16	1.00	1.00	1.00
17	1.00	1.00	1.00
18	3.00	4.00	1.00
19	3.00	3.00	1.00
20	2.00	4.00	1.00
21	1.00	1.00	3.00
22	3.00	1.00	1.00
23	1.00	1.00	1.00
24	1.00	1.00	1.00
25	1.00	1.00	1.00
26	1.00	1.00	1.00
27	1.00	3.00	1.00
28	1.00	3.00	1.00
29	1.00	1.00	1.00
30	1.00	1.00	3.00
31	3.00	4.00	1.00
32	3.00	3.00	1.00
33	1.00	1.00	1.00
34	1.00	1.00	1.00
35	1.00	3.00	1.00
36	1.00	1.00	1.00
37	2.00	1.00	3.00

7/17/18 6:15 PM 2/24

merged data all case and control together.sav

	Recreationa drug_use	SSRIs	Dosage	When_starte	When_stopp d	Restarted
1	1.00	1.00	20.00	1.00	2.00	1.00
2	1.00	2.00	60.00	1.00	5.00	3.00
3	1.00	3.00	200.00	1.00	2.00	1.00
4	1.00	1.00	20.00	1.00	5.00	3.00
5	1.00	1.00	20.00	1.00	5.00	3.00
6	1.00	1.00	20.00	1.00	1.00	1.00
7	1.00	1.00	20.00	1.00	2.00	1.00
8	1.00	3.00	50.00	1.00	5.00	3.00
9	1.00	1.00	40.00	1.00	1.00	1.00
10	1.00	3.00	50.00	1.00	2.00	1.00
11	1.00	3.00	50.00	1.00	5.00	3.00
12	1.00	3.00	150.00	1.00	5.00	3.00
13	1.00	3.00	50.00	3.00	5.00	3.00
14	1.00	4.00	20.00	2.00	5.00	3.00
15	1.00	3.00	20.00	1.00	4.00	2.00
16	1.00	4.00	20.00	2.00	5.00	3.00
17	1.00	1.00	10.00	1.00	5.00	3.00
18	1.00	3.00	100.00	1.00	4.00	2.00
19	1.00	2.00	20.00	2.00	5.00	3.00
20	1.00	3.00	100.00	2.00	5.00	3.00
21	1.00	3.00	50.00	1.00	5.00	3.00
22	1.00	1.00	20.00	2.00	5.00	3.00
23	1.00	3.00	50.00	1.00	5.00	3.00
24	1.00	2.00	20.00	1.00	5.00	3.00
25	1.00	3.00	50.00	1.00	5.00	3.00
26	1.00	1.00	10.00	1.00	5.00	3.00
27	1.00	2.00	200.00	1.00	2.00	1.00
28	1.00	2.00	20.00	1.00	5.00	3.00
29	1.00	3.00	50.00	1.00	5.00	3.00
30	1.00	3.00	50.00	1.00	5.00	3.00
31	1.00	1.00	20.00	1.00	5.00	3.00
32	1.00	2.00	20.00	1.00	2.00	1.00
33	1.00	3.00	100.00	1.00	2.00	1.00
34	1.00	2.00	20.00	2.00	5.00	3.00
35	1.00	3.00	25.00	1.00	5.00	3.00
36	1.00	3.00	100.00	1.00	5.00	3.00
37	1.00	1.00	10.00	1.00	4.00	2.00

merged data all case and control together.sav

	Was_the_SS RI_changed	Was_the_SS RI_dose_inc easad	other_meds	Family_hx
1	2.00	1.00	2.00	7.00
2	2.00	2.00	9.00	1.00
3	2.00	2.00	7.00	4.00
4	2.00	1.00	2.00	10.00
5	1.00	2.00	9.00	8.00
6	2.00	2.00	2.00	1.00
7	1.00	2.00	1.00	11.00
8	1.00	2.00	1.00	1.00
9	2.00	1.00	3.00	1.00
10	2.00	2.00	3.00	1.00
11	1.00	2.00	3.00	2.00
12	2.00	2.00	3.00	3.00
13	2.00	2.00	3.00	1.00
14	1.00	2.00	1.00	11.00
15	2.00	2.00	1.00	2.00
16	1.00	2.00	7.00	2.00
17	2.00	2.00	1.00	1.00
18	2.00	1.00	5.00	9.00
19	2.00	2.00	1.00	5.00
20	2.00	2.00	2.00	6.00
21	2.00	2.00	2.00	12.00
22	2.00	2.00	2.00	12.00
23	1.00	2.00	12.00	1.00
24	1.00	2.00	5.00	1.00
25	2.00	1.00	5.00	7.00
26	2.00	2.00	3.00	13.00
27	2.00	2.00	1.00	13.00
28	1.00	2.00	1.00	6.00
29	2.00	1.00	1.00	6.00
30	2.00	2.00	1.00	6.00
31	2.00	2.00	1.00	7.00
32	2.00	2.00	7.00	7.00
33	2.00	1.00	2.00	7.00
34	2.00	2.00	9.00	6.00
35	2.00	2.00	12.00	6.00
36	2.00	2.00	3.00	1.00
37	2.00	2.00	1.00	11.00

merged data all case and control together.sav

	Antenatal_US	Gender_of_neonate	Birth_weigh	Gestational_age
1	1.00	1.00	3.68	41.30
2	2.00	2.00	3.64	39.40
3	1.00	1.00	4.07	40.00
4	3.00	2.00	2.87	38.00
5	1.00	1.00	2.88	38.00
6	2.00	2.00	3.06	39.00
7	1.00	2.00	2.73	39.60
8	2.00	1.00	3.39	40.00
9	2.00	1.00	2.61	38.70
10	1.00	1.00	3.45	40.90
11	1.00	1.00	3.22	37.70
12	1.00	2.00	2.90	37.80
13	1.00	1.00	2.92	37.40
14	1.00	2.00	2.92	38.30
15	1.00	2.00	3.13	38.00
16	1.00	2.00	3.28	40.00
17	1.00	1.00	3.42	39.00
18	1.00	1.00	3.02	41.90
19	1.00	2.00	2.86	37.00
20	1.00	1.00	2.88	39.00
21	1.00	2.00	3.21	40.00
22	1.00	2.00	3.67	40.30
23	1.00	1.00	3.58	40.00
24	2.00	1.00	3.74	40.40
25	2.00	1.00	3.95	39.60
26	3.00	1.00	3.45	37.90
27	1.00	2.00	3.11	39.10
28	1.00	1.00	4.50	41.30
29	1.00	2.00	4.43	39.90
30	1.00	1.00	2.33	37.70
31	2.00	1.00	3.76	41.70
32	2.00	2.00	3.00	38.10
33	2.00	1.00	3.81	39.70
34	2.00	2.00	3.22	40.40
35	2.00	1.00	4.24	37.80
36	1.00	1.00	3.09	37.30
37	2.00	1.00	2.27	39.00

7/17/18 6:15 PM 5/24

merged data all case and control together.sav

	Mode_of_delivery	Why_Abx_started	Blood_culture_nega
1	1.00		
2	3.00		
3	1.00		
4	3.00		
5	3.00		
6	1.00		
7	2.00		
8	2.00		
9	1.00		
10	2.00		
11	1.00		
12	1.00		
13	1.00		
14	3.00		
15	3.00		
16	3.00		
17	1.00		
18	1.00		
19	1.00		
20	1.00		
21	1.00		
22	3.00		
23	1.00		
24	3.00		
25	3.00		
26	1.00		
27	1.00		
28	1.00		
29	1.00		
30	3.00		
31	3.00		
32	1.00		
33	1.00		
34	3.00		
35	3.00		
36	1.00		
37	3.00		

7/17/18 6:15 PM 6/

APPENDIX R

merged data all case and control together.sav

	Neonatal_problem	Neonatal_exam	Mode_of_fe ing	Age_at_ECG
1	1.00	1.00	2.00	48.00
2	1.00	1.00	1.00	48.00
3	1.00	2.00	3.00	48.00
4	1.00	1.00	2.00	50.00
5	1.00	1.00	2.00	48.00
6	1.00	2.00	1.00	48.00
7	1.00	1.00	1.00	50.00
8	5.00	1.00	3.00	70.00
9	5.00	2.00	2.00	48.00
10	1.00	1.00	3.00	48.00
11	1.00	1.00	1.00	48.00
12	4.00	1.00	1.00	56.00
13	1.00	4.00	1.00	48.00
14	1.00	1.00	1.00	48.00
15	1.00	4.00	2.00	48.00
16	4.00	2.00	2.00	48.00
17	4.00	1.00	1.00	48.00
18	1.00	3.00	2.00	59.00
19	1.00	1.00	2.00	50.00
20	1.00	2.00	1.00	61.00
21	1.00	1.00	2.00	70.00
22	1.00	1.00	2.00	49.00
23	2.00	1.00	1.00	48.00
24	5.00	1.00	1.00	48.00
25	1.00	1.00	1.00	48.00
26	1.00	1.00	2.00	48.00
27	2.00	1.00	3.00	54.00
28	2.00	1.00	3.00	48.00
29	1.00	2.00	1.00	48.00
30	2.00	1.00	3.00	62.00
31	1.00	1.00	3.00	49.00
32	5.00	1.00	2.00	62.00
33	1.00	1.00	2.00	52.00
34	1.00	1.00	2.00	52.00
35	5.00	1.00	3.00	65.00
36	5.00	3.00	2.00	49.00
37	2.00	1.00	3.00	61.00

merged data all case and control together.sav

	ECG_machine_QTc	Manually_calculated_QT	follow_up	QTcabove440msecs	var
1	339.00	400.00	2.00	.00	
2	415.00	404.00	2.00	.00	
3	345.00	388.00	2.00	.00	
4	372.00	361.00	2.00	.00	
5	400.00	388.00	2.00	.00	
6	375.00	368.00	2.00	.00	
7	375.00	378.00	2.00	.00	
8	362.00	388.00	2.00	.00	
9	362.00	388.00	2.00	.00	
10	363.00	354.00	2.00	.00	
11	343.00	359.00	2.00	.00	
12	378.00	375.00	2.00	.00	
13	402.00	390.00	2.00	.00	
14	318.00	358.00	2.00	.00	
15	363.00	364.00	2.00	.00	
16	316.00	349.00	2.00	.00	
17	388.00	362.00	2.00	.00	
18	398.00	381.00	2.00	.00	
19	415.00	433.00	2.00	.00	
20	371.00	374.00	2.00	.00	
21	374.00	377.00	2.00	.00	
22	305.00	333.00	2.00	.00	
23	350.00	369.00	2.00	.00	
24	381.00	357.00	1.00	.00	
25	397.00	410.00	2.00	.00	
26	381.00	394.00	1.00	.00	
27	387.00	392.00	2.00	.00	
28	334.00	350.00	2.00	.00	
29	344.00	361.00	2.00	.00	
30	349.00	361.00	2.00	.00	
31	362.00	380.00	2.00	.00	
32	408.00	409.00	2.00	.00	
33	353.00	383.00	2.00	.00	
34	346.00	340.00	2.00	.00	
35	381.00	358.00	2.00	.00	
36	372.00	381.00	2.00	.00	
37	329.00	343.00	2.00	.00	

merged data all case and control together.sav

	Study_grou	Age	Ethnicity	Mental_Hea h_history	other_med_history
38	1.00	26.00	1.00	1.00	6.00
39	1.00	33.00	1.00	1.00	8.00
40	1.00	49.00	1.00	2.00	3.00
41	1.00	39.00	1.00	2.00	6.00
42	1.00	32.00	1.00	1.00	6.00
43	1.00	22.00	1.00	1.00	6.00
44	2.00	25.00	1.00	4.00	2.00
45	2.00	20.00	1.00	4.00	6.00
46	2.00	31.00	1.00	4.00	3.00
47	2.00	23.00	1.00	4.00	6.00
48	2.00	40.00	1.00	4.00	7.00
49	2.00	19.00	1.00	4.00	7.00
50	2.00	36.00	2.00	4.00	7.00
51	2.00	25.00	2.00	4.00	5.00
52	2.00	32.00	1.00	4.00	4.00
53	2.00	30.00	2.00	4.00	1.00
54	2.00	35.00	1.00	4.00	6.00
55	2.00	25.00	1.00	4.00	3.00
56	2.00	35.00	1.00	4.00	6.00
57	2.00	35.00	1.00	4.00	6.00
58	2.00	22.00	1.00	4.00	6.00
59	2.00	30.00	1.00	4.00	4.00
60	2.00	28.00	1.00	4.00	7.00
61	2.00	35.00	2.00	4.00	6.00
62	2.00	42.00	1.00	1.00	6.00
63	2.00	35.00	2.00	4.00	2.00
64	2.00	30.00	1.00	4.00	4.00
65	2.00	32.00	1.00	4.00	1.00
66	2.00	39.00	2.00	4.00	6.00
67	2.00	32.00	1.00	4.00	1.00
68	2.00	26.00	1.00	4.00	3.00
69	2.00	29.00	2.00	4.00	1.00
70	2.00	34.00	1.00	4.00	4.00
71	2.00	34.00	1.00	4.00	6.00
72	2.00	31.00	1.00	4.00	3.00
73	2.00	31.00	2.00	4.00	6.00
74	2.00	25.00	1.00	4.00	6.00

7/17/18 6:15 PM 9/24

merged data all case and control together.sav

	Smoking	partner_smoker	Alcohol_in_pregnan
38	3.00	1.00	3.00
39	2.00	1.00	1.00
40	1.00	1.00	3.00
41	1.00	3.00	1.00
42	1.00	1.00	1.00
43	1.00	1.00	1.00
44	1.00	1.00	1.00
45	1.00	1.00	1.00
46	2.00	1.00	1.00
47	1.00	1.00	1.00
48	1.00	1.00	1.00
49	1.00	1.00	1.00
50	1.00	1.00	1.00
51	2.00	3.00	1.00
52	1.00	1.00	1.00
53	1.00	1.00	1.00
54	1.00	1.00	3.00
55	1.00	1.00	1.00
56	1.00	1.00	1.00
57	1.00	1.00	1.00
58	1.00	1.00	1.00
59	1.00	1.00	1.00
60	1.00	1.00	1.00
61	1.00	1.00	1.00
62	1.00	1.00	1.00
63	1.00	1.00	1.00
64	1.00	1.00	1.00
65	1.00	1.00	1.00
66	1.00	1.00	1.00
67	2.00	1.00	1.00
68	1.00	1.00	1.00
69	1.00	1.00	1.00
70	1.00	1.00	1.00
71	1.00	1.00	1.00
72	1.00	1.00	1.00
73	1.00	1.00	1.00
74	1.00	3.00	1.00

7/17/18 6:15 PM 10/24

merged data all case and control together.sav

	Recreationa drug_use	SSRIs	Dosage	When_starte	When_stopp d	Restarted
38	1.00	3.00	50.00	2.00	5.00	2.00
39	1.00	3.00	100.00	1.00	5.00	3.00
40	1.00	2.00	50.00	2.00	5.00	3.00
41	1.00	2.00	20.00	1.00	5.00	3.00
42	1.00	3.00	50.00	1.00	5.00	3.00
43	1.00	3.00	50.00	4.00	5.00	3.00
44	1.00	5.00	.00	5.00	6.00	3.00
45	1.00	5.00	.00	5.00	6.00	3.00
46	2.00	5.00	.00	5.00	6.00	3.00
47	1.00	5.00	.00	5.00	6.00	3.00
48	1.00	5.00	.00	5.00	6.00	3.00
49	1.00	5.00	.00	5.00	6.00	3.00
50	1.00	5.00	.00	5.00	6.00	3.00
51	1.00	5.00	.00	5.00	6.00	3.00
52	1.00	5.00	.00	5.00	6.00	3.00
53	1.00	5.00	.00	5.00	6.00	3.00
54	1.00	5.00	.00	5.00	6.00	3.00
55	1.00	5.00	.00	5.00	6.00	3.00
56	1.00	5.00	.00	5.00	6.00	3.00
57	1.00	5.00	.00	5.00	6.00	3.00
58	1.00	5.00	.00	5.00	6.00	3.00
59	1.00	5.00	.00	5.00	6.00	3.00
60	1.00	5.00	.00	5.00	6.00	3.00
61	1.00	5.00	.00	5.00	6.00	3.00
62	2.00	5.00	.00	5.00	6.00	3.00
63	1.00	5.00	.00	5.00	6.00	3.00
64	1.00	5.00	.00	5.00	6.00	3.00
65	1.00	5.00	.00	5.00	6.00	3.00
66	1.00	5.00	.00	5.00	6.00	3.00
67	1.00	5.00	.00	5.00	6.00	3.00
68	1.00	5.00	.00	5.00	6.00	3.00
69	1.00	5.00	.00	5.00	6.00	3.00
70	1.00	5.00	.00	5.00	6.00	3.00
71	1.00	5.00	.00	5.00	6.00	3.00
72	1.00	5.00	.00	5.00	6.00	3.00
73	1.00	5.00	.00	5.00	6.00	3.00
74	1.00	5.00	.00	5.00	6.00	3.00

7/17/18 6:15 PM 11/24

merged data all case and control together.sav

	Was_the_SS RI_changed	Was_the_SS RI_dose_inc eased	other_meds	Family_hx
38	2.00	2.00	2.00	1.00
39	2.00	2.00	2.00	2.00
40	1.00	2.00	1.00	1.00
41	2.00	2.00	3.00	1.00
42	2.00	2.00	3.00	1.00
43	2.00	2.00	9.00	1.00
44	3.00	3.00	9.00	1.00
45	3.00	3.00	5.00	2.00
46	3.00	3.00	10.00	6.00
47	3.00	3.00	2.00	1.00
48	3.00	3.00	11.00	6.00
49	3.00	3.00	5.00	1.00
50	3.00	3.00	1.00	1.00
51	3.00	3.00	3.00	7.00
52	3.00	3.00	1.00	7.00
53	3.00	3.00	1.00	7.00
54	3.00	3.00	6.00	1.00
55	3.00	3.00	3.00	1.00
56	3.00	3.00	1.00	2.00
57	3.00	3.00	1.00	12.00
58	3.00	3.00	1.00	1.00
59	3.00	3.00	2.00	1.00
60	3.00	3.00	1.00	1.00
61	3.00	3.00	1.00	1.00
62	3.00	3.00	7.00	9.00
63	3.00	3.00	1.00	7.00
64	3.00	3.00	4.00	1.00
65	3.00	3.00	4.00	11.00
66	3.00	3.00	9.00	11.00
67	3.00	3.00	2.00	1.00
68	3.00	3.00	9.00	1.00
69	3.00	3.00	4.00	6.00
70	3.00	3.00	3.00	9.00
71	3.00	3.00	9.00	1.00
72	3.00	3.00	9.00	1.00
73	3.00	3.00	1.00	1.00
74	3.00	3.00	1.00	1.00

7/17/18 6:15 PM 12/

merged data all case and control together.sav

	Antenatal_US	Gender_of_neonate	Birth_weigh	Gestational_ge
38	1.00	1.00	3.13	40.10
39	2.00	2.00	3.00	39.10
40	2.00	1.00	3.40	38.60
41	1.00	2.00	3.53	40.90
42	1.00	2.00	3.93	41.60
43	1.00	1.00	4.09	40.70
44	1.00	1.00	3.58	38.70
45	1.00	2.00	2.89	38.00
46	1.00	1.00	3.48	38.00
47	1.00	2.00	3.03	39.90
48	1.00	2.00	3.54	39.10
49	2.00	1.00	3.35	39.70
50	1.00	1.00	3.24	39.70
51	1.00	1.00	3.95	41.70
52	2.00	1.00	3.32	39.90
53	1.00	1.00	3.07	41.50
54	1.00	2.00	2.77	38.00
55	1.00	1.00	4.23	40.90
56	1.00	2.00	3.69	40.00
57	2.00	2.00	4.32	41.90
58	2.00	1.00	4.02	40.00
59	1.00	2.00	3.42	40.70
60	2.00	1.00	3.86	40.30
61	1.00	2.00	3.55	40.40
62	1.00	1.00	4.56	40.00
63	1.00	2.00	3.55	41.00
64	1.00	2.00	3.71	37.30
65	1.00	1.00	2.75	37.00
66	1.00	1.00	2.98	39.90
67	1.00	1.00	2.71	38.70
68	1.00	1.00	3.35	39.00
69	1.00	2.00	2.95	38.70
70	1.00	2.00	3.32	40.30
71	1.00	1.00	2.77	37.00
72	1.00	2.00	2.92	37.00
73	1.00	1.00	4.28	42.10
74	1.00	1.00	3.28	41.30

merged data all case and control together.sav

	Mode_of_delivery	Why_Abx_started	Blood_culture_negat
38	1.00		
39	3.00		
40	3.00		
41	1.00		
42	3.00		
43	1.00		
44	3.00	1.00	1.00
45	1.00	1.00	1.00
46	1.00	2.00	1.00
47	2.00	5.00	1.00
48	3.00	4.00	1.00
49	1.00	1.00	1.00
50	2.00	6.00	1.00
51	3.00	1.00	1.00
52	1.00	1.00	1.00
53	2.00	3.00	1.00
54	1.00	2.00	1.00
55	3.00	5.00	1.00
56	1.00	1.00	1.00
57	3.00	1.00	1.00
58	3.00	1.00	1.00
59	1.00	6.00	1.00
60	2.00	1.00	1.00
61	3.00	3.00	1.00
62	3.00	1.00	1.00
63	2.00	3.00	1.00
64	3.00	1.00	1.00
65	2.00	3.00	1.00
66	1.00	3.00	1.00
67	1.00	3.00	1.00
68	1.00	6.00	1.00
69	1.00	1.00	1.00
70	2.00	3.00	1.00
71	1.00	4.00	1.00
72	2.00	2.00	1.00
73	2.00	1.00	1.00
74	2.00	1.00	1.00

merged data all case and control together.sav

	Neonatal_problem	Neonatal_exam	Mode_of_feeding	Age_at_ECG
38	5.00	1.00	1.00	62.00
39	1.00	1.00	1.00	48.00
40	4.00	1.00	1.00	49.00
41	5.00	1.00	1.00	48.00
42	3.00	1.00	3.00	53.00
43	1.00	4.00	2.00	49.00
44	1.00	1.00	1.00	56.00
45	1.00	1.00	1.00	55.00
46	1.00	1.00	1.00	53.00
47	3.00	1.00	2.00	58.00
48	1.00	1.00	1.00	49.00
49	1.00	3.00	2.00	54.00
50	1.00	1.00	1.00	54.00
51	1.00	1.00	1.00	52.00
52	1.00	2.00	2.00	48.00
53	1.00	1.00	1.00	65.00
54	1.00	1.00	3.00	57.00
55	1.00	1.00	1.00	59.00
56	1.00	3.00	1.00	56.00
57	1.00	4.00	1.00	51.00
58	1.00	1.00	1.00	52.00
59	1.00	1.00	1.00	50.00
60	1.00	3.00	3.00	60.00
61	2.00	4.00	3.00	60.00
62	2.00	1.00	1.00	69.00
63	2.00	1.00	3.00	50.00
64	1.00	1.00	3.00	70.00
65	1.00	4.00	3.00	52.00
66	1.00	1.00	1.00	51.00
67	2.00	1.00	3.00	61.00
68	4.00	1.00	2.00	56.00
69	1.00	4.00	3.00	62.00
70	2.00	1.00	3.00	64.00
71	1.00	1.00	1.00	49.00
72	2.00	1.00	3.00	63.00
73	2.00	2.00	1.00	66.00
74	1.00	1.00	1.00	68.00

7/17/18 6:15 PM 15/24

merged data all case and control together.sav

	ECG_machine_QTc	Manually_calculated_QT	follow_up	QTcabove440msecs
38	400.00	395.00	2.00	.00
39	417.00	419.00	2.00	.00
40	402.00	407.00	2.00	.00
41	372.00	380.00	2.00	.00
42	349.00	335.00	2.00	.00
43	401.00	399.00	2.00	.00
44	353.00	388.00	2.00	.00
45	368.00	422.00	2.00	.00
46	351.00	388.00	2.00	.00
47	355.00	381.00	2.00	.00
48	410.00	388.00	2.00	.00
49	371.00	388.00	2.00	.00
50	355.00	346.00	2.00	.00
51	386.00	381.00	2.00	.00
52	366.00	413.00	2.00	.00
53	362.00	370.00	2.00	.00
54	410.00	390.00	2.00	.00
55	385.00	388.00	2.00	.00
56	341.00	408.00	2.00	.00
57	394.00	324.00	2.00	.00
58	359.00	348.00	2.00	.00
59	361.00	390.00	2.00	.00
60	371.00	374.00	2.00	.00
61	334.00	340.00	2.00	.00
62	398.00	406.00	2.00	.00
63	391.00	384.00	2.00	.00
64	373.00	366.00	2.00	.00
65	371.00	394.00	2.00	.00
66	416.00	416.00	2.00	.00
67	384.00	395.00	2.00	.00
68	367.00	343.00	2.00	.00
69	378.00	380.00	2.00	.00
70	399.00	392.00	2.00	.00
71	370.00	405.00	2.00	.00
72	348.00	363.00	2.00	.00
73	416.00	435.00	2.00	.00
74	402.00	407.00	2.00	.00

7/17/18 6:15 PM

merged data all case and control together.sav

	Study_group	Age	Ethnicity	Mental_Health_history	other_med_history
75	2.00	32.00	1.00	4.00	1.00
76	2.00	23.00	1.00	4.00	4.00
77	2.00	32.00	1.00	4.00	9.00
78	2.00	33.00	1.00	4.00	6.00
79	2.00	34.00	2.00	4.00	8.00
80	2.00	39.00	1.00	4.00	1.00
81	2.00	31.00	2.00	4.00	6.00
82	2.00	34.00	1.00	4.00	8.00
83	2.00	28.00	1.00	4.00	6.00
84	2.00	32.00	1.00	4.00	4.00
85	2.00	30.00	2.00	4.00	1.00
86	2.00	19.00	2.00	4.00	8.00
87	2.00	33.00	2.00	4.00	6.00
88	2.00	32.00	1.00	4.00	8.00

merged data all case and control together.sav

	Smoking	partner_smoker	Alcohol_in_pregnan
75	1.00	1.00	1.00
76	1.00	1.00	1.00
77	1.00	1.00	1.00
78	1.00	1.00	1.00
79	1.00	3.00	1.00
80	1.00	1.00	1.00
81	1.00	1.00	1.00
82	1.00	1.00	1.00
83	1.00	1.00	1.00
84	3.00	1.00	3.00
85	1.00	3.00	1.00
86	1.00	1.00	1.00
87	1.00	1.00	1.00
88	1.00	1.00	1.00

merged data all case and control together.sav

	Recreational drug_use	SSRIs	Dosage	When_started	When_stopped	Restarted
75	1.00	5.00	00	5.00	6.00	3.00
76	1.00	5.00	00	5.00	6.00	3.00
77	1.00	5.00	00	5.00	6.00	3.00
78	1.00	5.00	00	5.00	6.00	3.00
79	1.00	5.00	00	5.00	6.00	3.00
80	1.00	5.00	00	5.00	6.00	3.00
81	1.00	5.00	00	5.00	6.00	3.00
82	1.00	5.00	00	5.00	6.00	3.00
83	1.00	5.00	00	5.00	6.00	3.00
84	1.00	5.00	00	5.00	6.00	3.00
85	1.00	5.00	00	5.00	6.00	3.00
86	1.00	5.00	00	5.00	6.00	3.00
87	1.00	5.00	00	5.00	6.00	3.00
88	1.00	5.00	00	5.00	6.00	3.00

merged data all case and control together.sav

	Was_the_SSRI_changed	Was_the_SSRI_dose_increased	other_meds	Family_hx
75	3.00	3.00	4.00	6.0
76	3.00	3.00	2.00	6.0
77	3.00	3.00	1.00	1.0
78	3.00	3.00	2.00	1.0
79	3.00	3.00	7.00	7.0
80	3.00	3.00	1.00	7.0
81	3.00	3.00	1.00	1.0
82	3.00	3.00	3.00	2.0
83	3.00	3.00	3.00	5.0
84	3.00	3.00	3.00	7.0
85	3.00	3.00	9.00	1.0
86	3.00	3.00	1.00	1.0
87	3.00	3.00	9.00	1.0
88	3.00	3.00	1.00	10.0

merged data all case and control together.sav

	Antenatal_US	Gender_of_neonate	Birth_weight	Gestational_age
75	2.00	2.00	3.32	39.60
76	1.00	2.00	3.36	41.10
77	1.00	1.00	3.39	39.40
78	1.00	2.00	3.27	42.00
79	1.00	1.00	3.35	38.70
80	1.00	2.00	3.23	40.40
81	1.00	1.00	3.54	40.70
82	1.00	2.00	3.93	40.40
83	1.00	1.00	3.88	39.00
84	2.00	2.00	3.37	39.40
85	1.00	2.00	3.35	41.30
86	2.00	2.00	3.50	38.90
87	1.00	2.00	2.96	40.10
88	2.00	2.00	2.41	38.40

merged data all case and control together.sav

	Mode_of_delivery	Why_Abx_started	Blood_culture_negat
75	3.00	1.00	1.00
76	3.00	1.00	1.00
77	1.00	1.00	1.00
78	3.00	1.00	1.00
79	1.00	1.00	1.00
80	1.00	4.00	1.00
81	2.00	1.00	1.00
82	3.00	3.00	1.00
83	3.00	5.00	1.00
84	1.00	5.00	1.00
85	3.00	3.00	1.00
86	2.00	1.00	1.00
87	2.00	3.00	1.00
88	1.00	3.00	1.00

merged data all case and control together.sav

	Neonatal_problem	Neonatal_exam	Mode_of_feeding	Age_at_ECG
75	1.00	1.00	1.00	52.00
76	1.00	1.00	1.00	64.00
77	1.00	1.00	3.00	58.00
78	1.00	1.00	1.00	58.00
79	1.00	3.00	1.00	65.00
80	1.00	1.00	1.00	53.00
81	1.00	2.00	3.00	62.00
82	1.00	1.00	2.00	48.00
83	1.00	1.00	3.00	57.00
84	1.00	1.00	1.00	58.00
85	1.00	3.00	3.00	56.00
86	1.00	1.00	2.00	62.00
87	1.00	1.00	1.00	57.00
88	1.00	1.00	2.00	66.00

merged data all case and control together.sav

	ECG_machine_QTc	Manually_calculated_QT	follow_up	QTcabove440msecs	var
75	366.00	382.00	2.00	.00	
76	388.00	394.00	2.00	.00	
77	352.00	374.00	2.00	.00	
78	338.00	378.00	2.00	.00	
79	396.00	388.00	2.00	.00	
80	374.00	382.00	2.00	.00	
81	383.00	385.00	2.00	.00	
82	344.00	347.00	2.00	.00	
83	321.00	384.00	2.00	.00	
84	398.00	408.00	2.00	.00	
85	357.00	348.00	2.00	.00	
86	349.00	363.00	2.00	.00	
87	343.00	348.00	2.00	.00	
88	328.00	329.00	2.00	.00	

Appendix S Communication with and Confirmation of Ethical Approval from South West-Exeter Research Ethics Committee

NHS
Health Research Authority
South West - Exeter Research Ethics Committee
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1335
Fax:0117 342 0445

11 November 2015

Ms Marie Lindsay-Sutherland
Lead Advanced Neonatal Nurse Practitioner
[redacted]Hospital NHS Trust Hospital,
[redacted]

Dear Ms Lindsay-Sutherland

Study Title:	**Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?**
REC reference:	**15/SW/0310**
Protocol number:	**N/A**
IRAS project ID:	**148564**

The Research Ethics Committee reviewed the above application at the meeting held on 05 November 2015. Thank you for attending to discuss the application.

Provisional opinion

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

1. It was noted that the Israeli study had a bigger effect. Members queried whether this study was more likely to be a cohort study rather than a case control study as it might affect the analysis.

2. Members thought consideration should be given to the ECG being undertaken on all babies, and then be separated into those who were exposed to SSRI and those who were not.

3. Confirmation was required that only those over 18yr would be included in the study.

4. Members were disappointed that the supervisor had not accompanied you.

5. The participant information sheet:
   - included forceful statements: e.g. "if you allow your baby to take part…" and should be re-worded.
   - It needed to be re-written in language that was easily understood by a lay person.
   - Risks and benefits should be made more explicit.
   - It should be explained that confidentiality could be broken should disturbing information come to light, along with steps that would be taken should this occur.
   - Contact details for PALs should be provided at the end of the PIS.
   - How much time participants would have to consider taking part in the study should be defined.
   - It is stated that "SSRI **will** cause…" this should be changed to "**may cause…"**
   - It was noted that results of the study would be provided on the Internet: details of how to access this should be included.
   - The name of our Committee should be included as "South West – Exeter Research Ethics Committee".
   - There should be a footer on the PIS/CF stating one copy would be available for the participant to keep.
   - It was stated that the study would not cause delay in discharge, but mothers would have to wait for results: this should be clearly stated.
   - Abnormal results would be very upsetting. Even if the ECG was normal, this did not necessarily mean it would stay normal. This needed to be carefully worded (without alarming the mother).

6. The consent form:
   - Should include specific permission to inform their GP of their participation in the study.
   - Consent to supply the GP with a summary of the study and any findings should be obtained.

Guidance on composing information sheets and consent forms was available at:
(http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/)
http://hra-decisiontools.org.uk/consent/content-sheet.html

7. The Letter of invitation
   - Details relating to the supervisor should be removed and included in the PIS.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Mrs Nathoo (0117 342 1335) in the first instance.

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link:
http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 11 December 2015.

Summary of the discussion at the meeting

- **Social or scientific value; scientific design and conduct of the study**

  Members asked if this was a cohort study rather than a case control study.
  You stated it was the latter.

  Members wanted to know who had helped you with this study.
  The lead neonatal consultant at work had helped. This study was based on an Israeli study looking at babies with heart murmur, and those whose mothers had been exposed to antidepressants.

  Members asked if different antidepressants had different effects.
  You said you would be examining those on the same class of drug. Substance abusers would be excluded.

  It was pointed out that the control group was not "normal" but those suspected of requiring antibiotics. Members wondered whether antibiotics (particularly macrolides) could contribute to a longer QT interval.

Members wanted to know whether there would be confounding factors.
You advised that antibiotic therapy did not affect the heart, hence the inclusion of babies who were at risk, but had proved to be well.

It was not clear what the sample size was based on, as it did not match the outcome measured in the application.
The statistician at the University of Southampton had taken the results of the Israeli study into consideration, and advised 121 subjects in each group would be required.

It was queried whether there was a minimum duration of exposure to SSRI before mothers could be included.
Mothers could have taken SSRI for any length of time. A mood test would have been undertaken by the midwives during pregnancy and the mother would have been sent to the GP, and followed up regularly. There would be an alert that the woman was pregnant and on SSRI.

It was queried whether SSRI exposure would affect the baby in the womb.
You replied that exposure during early pregnancy (first 12 weeks) could affect the baby. After 12 weeks the foetus would just grow. In later pregnancy, SSRI exposure would be more likely to result in withdrawal symptoms. Exposure at the beginning and at the end of the pregnancy made the baby think it was still inside the womb. Data could be broken down to capture length of exposure. The point at which SSRI was taken in pregnancy would be included.

Upon query, you confirmed that in the first instance the ECG machine would interpret the results. The way the heart beats in the first days of life was very different. The cardiologist was happy with the study. A manual reading would be conducted within 24 hours.

- **Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity**

Members queried whether there was a risk of an allergic reaction to using pads/gel for the ECG.
Members were reassured that anti-allergenic gel would be used, which came off readily.

When asked, you confirmed data collection forms would initially be stapled to the consent form; once coded they would be separated.

- **Recruitment arrangements and access to health information, and fair participant selection**

The IRAS form stated 16yr olds could be included; the poster stated 18yr. Members requested confirmation of the inclusion age.
*You advised 16yr olds could be consented although there would not be many who were 16yr old **and** on SSRI.*

Members strongly recommended inclusion of 18yr and over as this would provide better protection to the mother.

Members wondered whether the consenting procedure could be undertaken within five minutes as stated.
Members were reassured that the potential participant would already have received the information sheet and would have had time to consider the information. Staff members were available round the clock should the participant have any questions. The completion and signing of the consent form would be to ensure they were happy to take part.

- **Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)**

It was unclear to the Committee whether women on SSRI would be aware of the potential side effects on their baby. If not, presenting them with the participant information sheet could be alarming. They should have been alerted to the potential dangers, but this might not have actually happened.
You stated that a plan of care would have been initiated and relevant information conveyed to the mother. Risks of withdrawal; abnormality; etc. would have been discussed with the midwife.

- **Informed consent process and the adequacy and completeness of participant information**

Changes required to the participant information sheet, consent form and letter of invitation are detailed at the beginning of the letter.

Upon query, you confirmed that the GP would be informed of their patient's participation.
Members asked for the consent form to include specific permission for this.

You advised that a summary of the study would be generated. Anything that occurred in hospital would be included and a copy of this made available to the GP.
Members asked for this to be included in the consent form as well.

The Committee requested for the participant information sheet to be simplified as it was quite complex and might be beyond the average woman.
The applicant agreed to comply.

- **Other general comments**

When asked, you confirmed this study had not previously been reviewed by a research ethics committee. You also confirmed that you had spoken to the R&D and leads of the relevant departments. The ECG would be conducted in the Maternity Unit and would provide an opportunity to consolidate practice. The midwives were happy to take part in the research.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.
Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [standardised communication with GP for discharge letter]	1	26 July 2015
IRAS Checklist XML [Checklist_02102015]		02 October 2015
IRAS Checklist XML [Checklist_22102015]		22 October 2015
Letter from statistician [Summary of discussion with statisician]	1	14 March 2015
Letters of invitation to participant [letter of invitation]	3	25 July 2015
Other [CV Mike Hall]	1	18 June 2015
Other [CV Helen Rushforth]	1	17 March 2015
Other [ERGO peer review feedback]	1	10 February 2015
Other [risk assessment for ethics]	1	20 January 2015
Other [neonatal ALERT form]	1	18 January 2015
Other [Data collection sheet SSRI users]	4	24 July 2015
Other [Data collection sheet non SSRI users]	4	24 July 2015
Other [standardised communication for electronic hospital system]	1	26 July 2015
Other [Poster for maternity staff]	2	24 July 2015
Participant consent form [Case Consent form]	4	22 October 2015
Participant consent form [Control Consent Form]	4	22 October 2015
Participant information sheet (PIS) [PIS case group SSRI users]	version 6	13 October 2015
Participant information sheet (PIS) [PIS control group non SSRI users]	6	13 October 2015
REC Application Form [REC_Form_02102015]		02 October 2015
Research protocol or project proposal [Protocol 29072015]	3	29 July 2015
Summary CV for Chief Investigator (CI) [CV Marie Lindsay-Sutherland]	1	14 March 2015
Summary CV for supervisor (student research) [CV Elizabeth Cluett]	1	01 April 2015

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

A Research Ethics Committee established by the Health Research Authority

15/SW/0310	Please quote this number on all correspondence

Yours sincerely

pp. Dr Denise Sheehan
Chair

Email: nrescommittee.southwest-exeter@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Miss Mary Burrows, [redacted] Hospital NHS Foundation Trust*

A Research Ethics Committee established by the Health Research Authority

NHS
Health Research Authority
South West - Exeter Research Ethics Committee
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1335
Fax:0117 342 0445

16 December 2015

Ms Marie Lindsay-Sutherland
Lead Advanced Neonatal Nurse Practitioner
Hospital NHS Trust Hospital,

Dear Ms Lindsay-Sutherland

Study title:	**Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?**
REC reference:	**15/SW/0310**
Protocol number:	**N/A**
IRAS project ID:	**148564**

Thank you for your letter of 10 December 2015 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Naazneen Nathoo, nrescommittee.southwest-exeter@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity letter]	1	13 October 2015
GP/consultant information sheets or letters [standardised communication with GP for discharge letter]	1	26 July 2015
IRAS Checklist XML [Checklist_02102015]		02 October 2015
IRAS Checklist XML [Checklist_22102015]		22 October 2015
IRAS Checklist XML [Checklist_10122015]		10 December 2015
Letter from statistician [Summary of discussion with statisician]	1	14 March 2015
Letters of invitation to participant [Letter of invitation]	4	25 November 2015
Other [CV Mike Hall]	1	18 June 2015
Other [CV Helen Rushforth]	1	17 March 2015
Other [ERGO peer review feedback]	1	10 February 2015
Other [risk assessment for ethics]	1	20 January 2015
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Other [Data collection sheet non SSRI users]	4	24 July 2015
Other [standardised communication for electronic hospital system]	1	26 July 2015
Other [Poster for maternity staff]	2	24 July 2015
Other [Response to ethics committee comments]	1	10 December 2015
Participant consent form [Case consent form]	5	14 November 2015
Participant consent form [Control Consent Form]	5	14 November 2015
Participant information sheet (PIS) [PIS Exposed Case]	7	25 November 2015
Participant information sheet (PIS) [PIS Unexposed ontrol]	7	25 November 2015
REC Application Form [REC_Form_02102015]		02 October 2015
Research protocol or project proposal [Protocol 29072015]	3	29 July 2015
Research protocol or project proposal [Protocol 08122015]	4	08 December 2015
Summary CV for Chief Investigator (CI) [CV Marie Lindsay-Sutherland]	1	14 March 2015
Summary CV for supervisor (student research) [CV Elizabeth Cluett]	1	01 April 2015

Appendix T Table Demonstrating the Sample Size for Desired Width- Intra-Rater Correlations (Bonett, 2002)

repeated measures	K	2	
Intraclass correlation (rough estimate)	P	0.8	
Confidence Interval %	A	95	
desired width of confidence interval	W	0.2	
sample	N	XX	

Appendix U Confirmation of District General Hospital Approval to Host Research Study

[ ] Hospital NHS
NHS Foundation Trust
Research & Innovation

30 December 2015

Marie Lindsay-Sutherland
[ ] Hospital NHS Foundation Trust

Dear Marie

Re: **Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?**
REC reference number: 15/SW/0310
Protocol Ref: V4

We are pleased to advise that the above named research project has been reviewed against the Research Governance Framework for Health and Social Care (2005 2nd edition) and NHS permission for research has been granted to undertake the proposed project at [ ] Hospital NHS Foundation Trust.

Documents reviewed were in accordance with current versions listed in the favourable ethical opinion correspondence received from South West-Exeter Research Ethics Committee dated 16 December 2015.

Conditions under which this approval is granted can be found at
http://nww.intranet.[ ].nhs.uk/files/Conditions%20for%20Undertaking%20Research%20July%2014%20pdf.docx

Please notify the Research and Innovation Department if there are any changes in the above named study relating to these conditions.

Please see Appendix 1 outlining Trust Policy re: research income

Yours sincerely

Sarah Chessell

Sarah Chessell
Head of Research, Innovation, NICE and Clinical Audit

Cc: Sandra Chitty, Head of Midwifery
sacha.crowley@[ ].nhs.uk

Please send all correspondence relating to this study to:
Research & Innovation Department
[ ]

Appendix V Certificates of Achievement for Introduction to Good Clinical Practice eLearning (Secondary Care) and Informed Consent in Paediatric Research

National Institute for Health Research

Clinical Research Network

CERTIFICATE of ACHIEVEMENT

This is to certify that

Marie Lindsay-Sutherland

has completed the course

Introduction to Good Clinical Practice eLearning (Secondary Care)

January 25, 2016

Modules completed:

Introduction to Research in the NHS
Good Clinical Practice and Standards in Research
Study Set Up and Responsibilities
The Process of Informed Consent
Data Collection and Documentation
Safety Reporting

This course is worth 4 CPD credits

CPD
The CPD Certification Service

National Instit
Health Re

NHS
National Institute for Health Research
Clinical Research Network

CERTIFICATE of ACHIEVEMENT

This is to certify that

Marie Lindsay-Sutherland

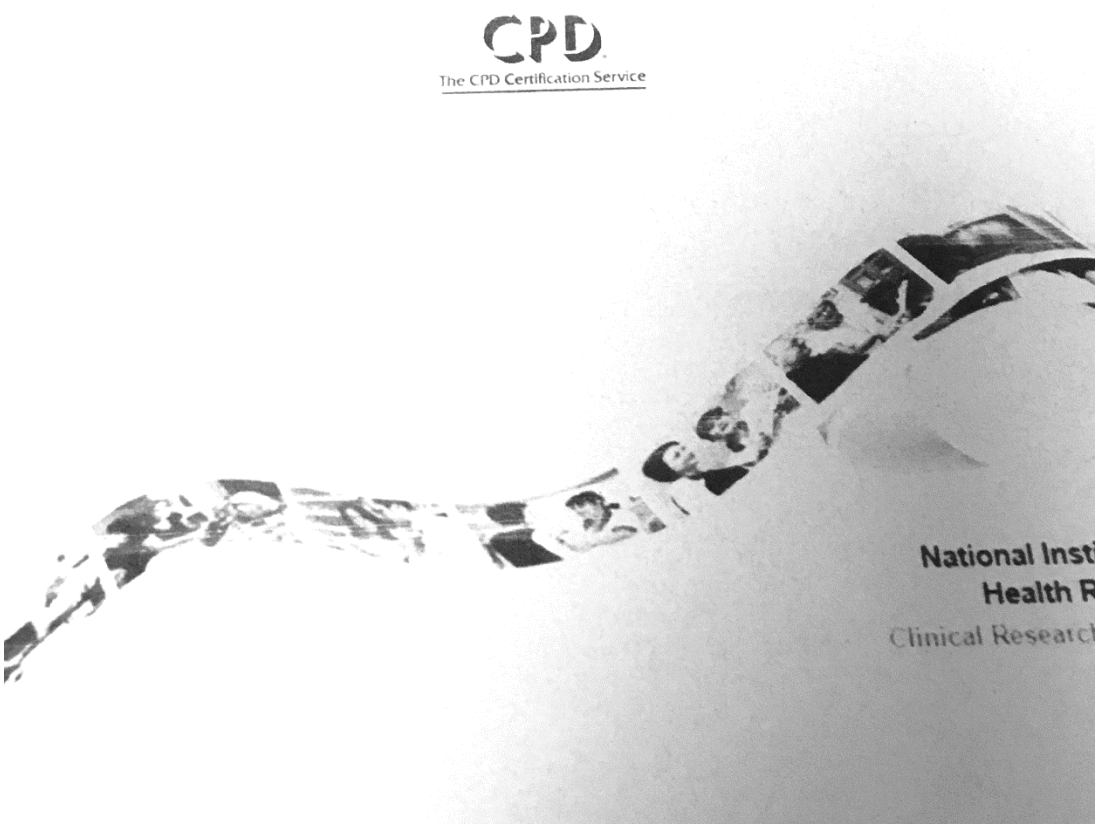
has completed the course

Informed Consent in Paediatric Research

January 24, 2016

This course is worth 1 CPD credit

CPD
The CPD Certification Service



Appendix W Risk Assessment Required by University of Southampton in Order to Provide Vicarious Liability for the Research Study

Health Sciences

UNIVERSITY OF Southampton

Research Risk Assessment Form

IMPORTANT
If you have any queries please contact the Faculty Health and Safety officer, Peter Fisk at P.Fisk@soton.ac.uk

Please read the following before completing this form

i. If this is a student project this risk assessment needs to be completed by the student (applicant) and supervisor (reviewer).
ii. If this is a staff project this risk assessment needs to be completed by the Principal Investigator (applicant) and reviewed by the head of the actual research programme/area/unit relevant to the proposal.
iii. If this is a staff project and the risk assessment is completed by a Research Assistant/Fellow, then it needs to be checked by the Principal Investigator and reviewed by the head of the actual research programme/area/unit relevant to the proposal. If the Principal Investigator is head of the actual research programme/area/unit relevant to the proposal, then the Director of Research needs to be the reviewer.
iv. If the Principal Investigator completes the risk assessment and the applicant is the head of the actual research programme/area/unit relevant to the proposal then it needs to be reviewed by the Director of Research (reviewer).
v. If you are an international student undertaking your research fieldwork entirely within your own country this risk assessment needs to be completed by you (applicant) and supervisor (reviewer)

Once complete, the risk assessment form should be uploaded via the University Ethics system ERGO at www.ergo.soton.ac.uk

Applicant Name:	Marie Lindsay-Sutherland				
Project Title:	Is Prolongation of the QT Interval in Term Neonates (Greater Than 37 Complete Weeks Gestation) Associated with Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs)?				
Type of project: (Please tick or insert **X**)	**Staff**		**Student**	**X**	
Supervisor's Name: *(if relevant – see point i above)*	Elizabeth Cluett; Helen Rushforth; Michael Hall				
Principal Investigator's Name: *(if relevant- see point iii above)*	Marie Lindsay-Sutherland				
Who will this risk assessment/research involve: *(please provide a brief description of your proposed sample and/or research site)*	Neonates				

Where appropriate list the individuals doing the work	Advanced Neonatal Nurse Practitioners Midwives Practitioners trained in performing ECGs				
Does the work/research involve lone working: *(for example working outside of office hours in your office or a lab-based environment) or conducting interviews with subject in their own homes in which case please complete Forms RA2, RA3 and RA4 as necessary with this assessment.*	**Yes**		**No**	**X**	

Health & Safety Risk Assessment

Work task / activity	ECG in neonates at 48- 72 hours old.				
Assessor(s)	Marie Lindsay-Sutherlandl	**Responsible Manager**	Elizabeth Cluett; Helen Rushforth; Michael Hall	**Date**	20/01/2015
Faculty	Faculty of Health Sciences	**Academic Unit/Team**	Centre for Innovation and Leadership in Health Sciences	**Location**	X
Brief description of task / activity	This task forms a recognised.standard investigation for neonates. During this task small sticky pads, electrodes, are placed on to the neonate's chest and limbs. The electrical impulses of the heart are read via the electrodes and transformed into a graphic interpretation. This only takes10 seconds to achieve once the electrodes are in place and the baby is settled. The electrodes are then removed, and the baby is settled post procedure.				

Additional notes (e.g, references, persons at risk, risk factors, etc.) **[optional]**	This is a routine non-invasive NHS procedure. No significant risks were identified other than potential emotional distress of the parent/ person with parental responsibility, and some minor discomfort to the neonate from the attachment of the electrodes. No risk to the researcher or practitioner operating the ECG were identified, as all have been trained appropriately in its correct use

Declaration by responsible manager: I confirm that this is a suitable & sufficient risk assessment for the above work activity / task.

Signed		Print Name	Elizabeth Cluett	Date	20/01/2015

Hazards and reasonably foreseeable worst case consequences	Inherent risk (no controls) From matrix (mark with X)		Controls (measures to reduce risk)	Residual r (with contr From mat (mark with
Emotional distress	High		Support from health professionals antenatally/ postnatally Good communication with mothers regarding effects of SSRIs on fetus/ neonate Well informed health professionals regarding SSRIs effects on fetus/ neonate Informed consent regarding research	High
	Medium			Medium
	Low	X		Low

To be completed by the Reviewer

Can the risks be further reduced?				Further precautions/additional controls required	Date to be completed
YES		NO	x		

Reviewer name	Reviewer Signature	Date
Peter Fisk		23/01/2015

Appendix X Confirmation of University of Southampton Approval to Provide Vicarious Liability for the Research Study

University of
Southampton

Dr Elizabeth Cluett
Faculty of Health Sciences
University of Southampton

Date: 8th October 2015

Dear Dr Cluett,

Professional Indemnity and Clinical Trials Insurance

Project Title: Is Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) Associated with Prolongation of the QT Interval in Term Neonates (37 Complete Weeks Gestation or Greater)?

ERGO Ref: 8442

Participant Type	**Number of participants**	**Participant age group**
Patients	242	Minors

Thank you for submitting the completed questionnaire and attached papers.

Having taken note of the information provided, I can confirm that this project will be covered under the terms and conditions of the above policy, subject to written informed consent being obtained from the participating volunteers or their parent, guardian, next of kin as appropriate.

I would also advise that it is a condition of the University's insurance that any incidents that could eventually result in a claim are reported immediately. Serious adverse events, suspected unexpected serious adverse reactions and similar fall into this category. For studies hosted by or sponsored by UHS the Research and Development Office will copy the SAE and SUSAR reports they receive to the University Insurance Office. For all other studies such events must be reported to me at the same time as they are reported under the Protocol. Failure to do this could invalidate the insurance.

If there are any changes to the above details, please advise us as failure to do so may invalidate the insurance.
Yours sincerely

Mrs Jenny King
Senior Insurance Services Assistant

Tel: 023 8059 2417
email: jsk1n08@soton.ac.uk
Finance Department, University of Southampton, Highfield Campus, Southampton SO17 1BJ U.K.
Tel: +44(0)23 8059 5000 Fax: +44(0)23 8059 2195 www.southampton.ac.uk

Appendix Y Confirmation of Neonatal Matron Approval to Support Research Study

[ ] Hospital NHS
NHS Foundation Trust

[ ] – Matron Neonatal Unit
[ ] 448217
[ ]@[ ].nhs.uk

18 March 2015

To whom it may concern,

[ ]Hospital NHS Foundation Trust uses a two tier model for the medical staffing of the neonatal unit. This model includes the consultant and the advanced neonatal nurse practitioner. While the skills of the ANNP are pivotal to the everyday clinical care of the preterm and sick baby it is recognised that the practitioner also has a strategic role in influencing neonatal care at both a national and local level. Practice on the neonatal unit is informed by audit, research, benchmarking, guidelines and teaching.

The ANNP is expected to keep up-to-date and disseminate new developments in neonatal care, to act as a resource and mentor to less experienced staff.and be actively involved in clinical audit/ research projects.

I therefore support Marie Lindsay Sutherland in conducting a research project on the understanding that there is no impact on clinical care of the babies.

Yours Sincerely

[ ]

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