

### ***“Does IUI have a place in modern ART practice?”***

Infertility is defined as failure to achieve a pregnancy after 12 months of unprotected sexual intercourse according to the WHO definition. It affects 1 in 6 couples in the UK (NICE 2013), Australia and 1 in 10 couples in the USA (CDC data). WHO evaluation of Demographic and Health Surveys (DHS) data (2004), estimated that in developing countries one in every four couples experienced infertility (duration after 5 years).

The most common reasons for IVF treatment cycles being carried out were male infertility (37% of recorded reasons), unexplained (32%), an ovulatory disorder (13%), tubal disease (12%) and endometriosis (6%). (HFEA data 2018). The treatment modalities include OI, IUI and IVF/ICSI.

#### **Definition:**

IUI is an infertility treatment modality which involves the placement of the prepared sperm into the uterine cavity timed around ovulation. This can in combination with ovarian stimulation or in an unstimulated cycle. The aim of the stimulated cycle was to increase the number of follicles available for fertilisation and to enhance accurate timing of insemination in comparison to the natural cycle IUI.

#### ***Clinical Indications of IUI***

- Unexplained infertility
- Cervical factor
- Mild to moderate male factor infertility
- Mild endometriosis
- Unable to achieve pregnancy by vaginal intercourse due to psychosexual or organic causes
- Donor insemination- both same sex and heterosexual couples
- In viral disorders such as HIV to lower the risk of transmission
- Single lady

#### **Pre- requisites for IUI:**

1. At least one patent fallopian tube
2. Normal sperm parameters
3. Regular ovulatory cycles for unstimulated cycles
4. Age less than 40

### **HFEA data from 2014- 2016:**

DIUI is a well-established mode of treatment for women seeking fertility treatment either in a same sex relationship (41%), severe male factor e.g. Azoospermia (42%) or as a single lady (17%).

The proportion seeking treatment has increased by 10% and NHS funded cycles have also proportionately increased in Scotland, NI and Wales since 2014. DI birth rate was 12%, slightly better with stimulated cycles at 13% vs. 11% with unstimulated cycles.

In 2016, the IUI birth rate per treatment cycle was 12%. The rates of successful treatment cycles reduce for patients with increasing age and the birth rates across all age groups have remained broadly stable over time. The highest birth rates were in patients under 38 years of age (14% for under 35s, and 12% for patients aged 35–37). The rates of successful treatments reduce for patients over 42 years of age.

The multiple pregnancy rates for DI and IUI were 8% in 2016.

### **NICE guideline CG156- Fertility Problems: assessment and Treatment**

IUI is not recommended in couples with unexplained infertility, male factor and mild endometriosis unless the couples have religious, cultural or social objections to proceeding with IVF. This was widely thought to be based on the below two trials.

#### ***Bhattacharya trial bmj 2008 –***

This was a pragmatic randomised controlled trial comparing expected management, clomiphene citrate and unstimulated IUI in the management of unexplained infertility. 580 women were randomised to each of the group and followed up for 6months after randomisation. The primary outcomes measure was livebirth. This was 17% after EM, 14% after CC and 23% after unstimulated IUI. The acceptability rate was higher in the intervention group (cc-94% and IUI- 96%), in comparison to the expectant group (80%). The conclusion was that CC or IUI was unlikely to offer superior livebirths when compared to expectant management.

#### ***FASST trial Fertility Sterility 2007 Reindollar et al***

This was a randomised clinical trial to determine the value of gonadotrophin/IUI therapy for infertile women aged 21-39 years. The couples were randomised to receive either conventional treatment (n=247) with three cycles of CC/IUI, three cycles of FSH/IUI and up to six cycles of IVF or accelerated treatment (n=256) that omitted the three cycles of FSH/IUI. The primary objective was the time to livebirth and the cost effectiveness. An increased rate of pregnancy was observed in the accelerated arm HR 1.25 compared with conventional arm. Median time to pregnancy was 8 and 11 months in the respective arms. Per cycle pregnancy rates for CC/IUI were 7.6%, 9.8% with FSH/IUI and 30.7% with IVF. The study calculated a savings of \$2624 per couple for accelerated treatment. The study conclusion was that FSH/IUI treatment was of no added value.

## **Impact of NICE guideline CG156- Fertility Problems: assessment and Treatment**

This has impacted on the CCG funding and is reflected on the year on year decrease in the number of IUI procedures with a 50% decrease since 2013, as reported by the HFEA. This is despite the birth rate remaining constant at around 12%. There was a 20% drop in the number of clinics offering IUI as treatment.

This in sharp contrast to the surveys conducted post NICE publication.

**Nandi et al 2014 Human Fertility** – online survey of specialist opinion on first line management for unexplained subfertility. This was an email survey of 420 reproductive medicine practitioners, with a response rate of 32.38%. Of those who responded 39% agreed with the NICE and 25% did not agree and the remainder partially agreed. 27% felt that the guideline may influence a change of their practice. And 27% of the respondents were definite to change their practice and a similar number said they would not change their practice. Only 16% would offer IVF as the first choice of treatment as recommended by NICE. This confirmed the ongoing clinical uncertainty despite published guidelines.

### ***BMJ open 2015 D Kim, T Child, C Farquhar***

IUI: UK survey on the adherence to NICE clinical guidelines by fertility clinics. The aim of the online questionnaire survey was to evaluate the awareness and response of the fertility clinics to the change in the guideline. The survey email was sent to 82 UK fertility clinics. The response rate was 70% (46/66). 96% of the clinics (44/46) continued to offer IUI in April 2014, at the time of the survey with nearly all except one clinic offering ovarian stimulation. The most common method was using gonadotrophins, followed by clomiphene citrate and letrozole. Only a small proportion of clinics changed their practice significantly and reduced the number of IUI cycles.

The review will only consider IUI in the context of treatment option for unexplained infertility and mild male factor infertility.

### **Rationale behind IUI:**

Only 0.1% of spermatozoa reach the cervical canal 1 hr after upper vaginal insemination. Similarly, only 1 in 14 million motile sperm reached the site of fertilization in the oviduct after vaginal placement (**Settlage et al 1973**). The aim of IUI is to increase the gamete density at the site of fertilisation after the preparation of the sperms similar to that in IVF. This excludes the dead, immotile sperms, debris, white cells and seminal plasma which may interfere with fertilisation. IUI also bypasses the cervix which acts as a reservoir for the sperms.

Few of the evidence against the IUI was that the low success rates, lack of effectiveness and the higher risks of multiple pregnancy with up to 40% of multiple pregnancies thought to be

contributed by IUI. This mainly happened in the setting of gonadotrophin stimulation in clinics outside the EU.

However the advantage is that it is a relatively simple process and procedure to perform with the risk of OHSS being very low. The patient acceptability and compliance was high.

**Bensdorp AJ- Eur Journal Obstet Gynecol reprod Biol oct 2016-** analysed the dropout rates in couples undergoing IVF. There were comparable dropout rates between IVF- SET (single embryo transfer) group and the IUI-Os (ovarian stimulation) group. The dropout rate was almost twice as high in the IVF- MNC (modified natural cycle) group, predominantly driven by patient preferences. The risk of OHSS was very low in IUI.

### Donor IUI

**Cochrane review 2018** compared the routes of insemination and pregnancy outcomes in intra-cervical insemination (ICI) vs. intra- uterine insemination (IUI) in DI. The review included 6 RCT's with 708 women with each of the two studies comparing ICI and IUI between the unstimulated, gonadotrpip stimulated cycle and the timing. If LB was assumed to be 30% for OI ICI then it was between 24- 80% with OI IUI. There were higher multiple pregnancy rates in the stimulated cycles with no MPR into unstimulated cycles. The review concluded that there was insufficient evidence for difference in the outcomes or the timing between the two methods of insemination.

### IUI and male factor infertility

There is absence of clinically recognised definition for mild male factor sub fertility. Two or more semen analysis that have one or more variables which fall less than the 5<sup>th</sup> centiles as defined by WHO 2010.

**BFS guidelines for practise on sperm quality** acknowledges that the concentration of progressively motile sperms have shown to be the most predictive factor with regard to the outcome. It recommends that artificial insemination requires atleast  $5 \times 10^6$  million motile sperm, below which the pregnancy rates are likely to be lower. Predictors of pregnancy and live birth in couples with unexplained infertility and OI with IUI are baseline age, duration of infertility, income, and prior pregnancy loss (**Hansen et al 2016, Fertility and sterility**)

### **Cochrane review on=2016- ART for male subfertility cissen M, bensdorp A**

This was a review of 10 RCTS of 757 couples. The evidence was graded as low or very low. The primary outcome was livebirth and OHSS per couple randomised. 3 RCTS compared the LB in 364 couples who were randomised to IUI with OH vs IUI in natural cycle. The odds ratio for LB was 1.34 with no statistical difference. The odds ratio of 1.03 was achieved comparing eth two studies involving 86 couples between IVF and IUI+OH. The review concluded that there was insufficient evidence to determine whether there was any

difference in safety and effectiveness between different treatment options and that more research was needed.

### **IUI and unexplained sub fertility**

#### ***FAST Trial-***

#### ***TUI trial- Lancet 2018- C.Farquhar***

This was a pragmatic, open-label, RCT of women with unexplained infertility and an unfavourable prognosis of natural conception of <30% in the next 12 cycles, by the Hunault score. The women were randomly assigned (1:1) to 3 cycles of stimulated IUI (n=101) or 3 cycles of expectant management (n=100). The ovarian stimulation was either with clomiphene citrate (50 to 150mgs) or letrozole (2.5 to 7.5mgs). The primary outcome measure was cumulative livebirth in the intention to treat population. The results showed that the women in the IUI group had higher cumulative livebirth of 31% in comparison to 9% in the expectant group which was still the case even after the exclusions of all protocol violations. The livebirth rates were 27% vs 7%. There was no case of OHSS. The multiple pregnancy rate in this study was 6%. The study concluded that IUI with ovarian stimulation is a safe and effective treatment option with a three -fold improvement in livebirths over expectant management.

#### ***M-OVIN trial – lancet 2017 madelon van Wely***

Trial in women aged 18 or over with normogonadotrophic anovulation who achieved no pregnancy after 6 cycles of CC OI (up to a max dose of 150mg/day). The primary outcome was Live birth within 8 months of randomisation, achieved after a gestational age of 24 weeks.

666 women were assigned between 4 groups- CC with IUI (n=163), CC with intercourse (n=172), gonadotrophins with IUI (n=166) and gonadotrophins with intercourse (n=165). The live birth was better in the gonadotrophin stimulated group in comparison to the clomiphene citrate- 52% vs. 41% with RR 1.24. The addition of IUI however no additional benefit to the improvement of live birth.

#### ***Nandi et al fertility sterility 2017, June***

RCT comparing IUI with gonadotropin stimulation with IVF for treatment of unexplained subfertility. 207 couples were assigned to 3 cycles of IUI +COH or one cycle of IVF. Singleton livebirth in IUI was 24.7 % and 31% with IVF. NO OHSS in IUI vs 3.7% in IUI. MP/LB was 13.8% in IUI group compared to 8,3% in the IVF group contributed by one additional patient. The study authors concluded that the singleton livebirth rate was not significantly different between one cycle of IVF than 3 cycles of IUI+ COH.

#### ***Cochrane review on IUI for unexplained subfertility 2016 Feb., Veltman-Verhulst SM***

The review considered 14 trails involving 1867 women. The quality of these studies was rated low to moderate quality. Imprecision in the findings for livebirth and MPR. Stimulated IUI pregnancy outcomes were better in comparison to natural IUI, which were in turn better than TI (timed intercourse) in stimulated cycles. There was no difference in the MPR between the groups.

**Cochrane review 2016-Sarah Lensen** uncertain whether LEI (local endometrial injury) improves the probability of pregnancy and ongoing Pregnancy/Live birth in women undergoing IUI or natural conception.

### **Cost effectiveness:**

**Lobke M. Moolenaar, Ben Mol June 2015 reproductive biomedicine online**

Comparing the treatment modalities such as IUI, IVF and ICSI and the cost effectiveness for the treatment of male subfertility. If the prewash TMSC (total motile sperm count) was > 3million, the costs per livebirth are lower for IUI and with the reverse TMSC values, ICSI was more cost effective.

**Vanderpoel Cochrane review Nov 2010-** Cochrane review comparing the firm and soft catheters for IUI. The Odds ratio for clinical pregnancy from 6 RCTs was 1.0 between the two groups and the odds ratio for livebirth was 0.94 after review of 3 studies .no specific conclusion could be made regarding the superiority of one choice of catheter over the other. The review recommended that live birth should be reported as the primary outcome with additional measures such as miscarriages and discomfort in future studies.

### **Prognostic factors in IUI:**

**JBRA assisted reprod 2018 march** – retrospective study of 237 cycles of IUI. The study found that female age was inversely correlated with pregnancy rates( $P=0.0001$ ). the overall clinical pregnancy rate was low at 7.59%. the women who achieved a pregnancy was younger with an average age of 32.56 vs 36.64 years in women who failed to achieve a pregnancy. However, the clinical pregnancy was not statistically found to be affected by other variable such s causes of infertility, number of mature follicles or sperm with progressive motility.

The favourable factors for IUI were age <35 years, unexplained infertility, minimal endometriosis, sperm count >2.5 million in the day of IUI, which had a higher clinical pregnancy rate of 12.74%. the drawback of the study was that it failed to comment on the livebirth rates which was possibly the better outcome measure than the clinical pregnancy rate. The success rate from the centre was lower than the UK average.

### **Discussion:**

The HFEA acknowledges that it does not collect comprehensive information regarding the outcomes as it does for IVf and DI. This approach needs to be considered in the light of the current evidence so that more training and strict published protocols for ovarian stimulation are followed by the clinics. This will ensure that the couples benefit from best evidence based protocol treatment and maximise their chances of pregnancy. There will also be cost benefit to the cash strapped NHS if the couple achieve pregnancy through IUI. This has been established by the incremental cost effectiveness ratio published in recent studies.

The criticism also surrounds the fact that IUI does attract the same attention in comparison to IVF and has perhaps less investment in terms of research. However a review of the clinicaltrials.gov website revealed that there were 71 registered trials with 12 ongoing trials in IUI. This is encouraging and hopefully would expand the knowledge base and improve the outcomes with IUI. The particular trials of interest include the PRORAILS study looking at individualisation of stimulation doses in the future and the SUPER trial comparing gonadotrophin vs clomiphene citrate for stimulation in IUI.

The treating clinicians should be obliged to discuss the current evidence as NICE continues to consult on the addendum to the fertility guideline relating to IUI.

The evidence clearly proves that unstimulated IUI has role in DIUI but in other indications the success rates are no better than timed intercourse or expectant management. Unstimulated IUI has very limited indications in clinical practise. Though the HFEA data showed a slight increase in the LBR following stimulation with DI, the difference is too small to recommend stimulated DI routinely.

Offer of 3 cycles of stimulated IUI with mono follicular development should definitely be considered as a first step approach in the treatment of unexplained infertility in couples with unexplained infertility and poor prognosis to pregnancy in women younger than 38 years. More than 90% of the livebirths from IUI were achieved in the first two cycles of treatment. IVF before IUI-OS for this indication should be considered with caution in the light of the new evidence from good quality studies. It should be continued to be offered for women in same sex relationship. Due to the lack of standardised definition of mild male factor infertility it would need to be evaluated more to positively see the benefit from the treatment.

However, the emphasis should be strict cancellation policies in place with multi follicular development and the cautious use of gonadotrophins. Further research is urgently required to continually evaluate the treatment modality and thus improve the choices to the patient. We should perhaps take the treatment option more seriously as treating clinicians and treat the process with the same vigour and care as we would with IVF cycles. This approach may contribute to optimise the IUI outcomes.

Furthermore the burden of expensive IVF treatments should be considered alongside the potential savings with IUI cycles, particularly in the setting of developing countries. This may also be true for some of the developed countries either funded by private companies or with restrictions on funding allocation like in the NHS.