The nutritional role of amniotic fluid – clues from infants with congenital obstruction of the digestive tract

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ABSTRACT

AIMS

To investigate the role played by amniotic fluid in late fetal nutrition by analysis of infants born with digestive tract atresia.

METHODS

Birth weight, gestational age and gender of infants born with oesophageal (OA), duodenal (DA), jejunal (JA) and ileal atresia (IA) were recorded and birth weight (BW) Z-scores compared. Infants with incomplete obstruction (stenosis), chromosomal or syndromic conditions, and multiple congenital malformations were excluded. Term infants admitted with suspected postnatal intestinal obstruction in whom no congenital malformation was found were used as a control group.

RESULTS

A total of 584 infants were identified comprising 148 OA, 60 DA, 26 JA and 57 IA with 293 in the control group. Infants with OA and DA had statistically significantly lower BW Z-score than controls. However, BW Z-score for infants with more distal atresia (JA and IA) was similar to controls. When compared with infants with OA, BW Z-score for infants with more distal atresia was higher than that for OA. BW Z-score in infants with OA was significantly lower in those born at term compared to those born preterm (mean -0.92±SD1.0 *vs* -0.48±0.87; p=0.01) with a significant negative correlation between BW Z-score and increasing gestational age (R^2 = 0.12; p<0.0001). This effect of gestational age was not seen in other atresias.

CONCLUSION

These observations support the concept that reduced enteral absorption of amniotic fluid due to high digestive tract obstruction in utero reduces fetal growth. The effect is greater when the obstruction is more proximal and with advancing gestation.

Word count 249

What is known about this topic

- Animal studies suggest that that amniotic fluid provides 10-15% of the nutritional intake of the normal fetus in later pregnancy.
- Low birth weight has been noted in infants born with various levels of digestive tract obstruction.
- Birth weight z scores are reduced in infants with oesophageal atresia, the reduction being greater in term versus preterm infants

What this study adds

- We have confirmed a direct correlation between increased fetal maturity and reduced birth weight z scores in infants with oesophageal atresia
- Reduced birth weight z scores are also seen to a lesser extent in duodenal atresia but not in atresia beyond the duodenum
- Amniotic fluid plays an important role in late fetal nutrition and absorption appears to be in the stomach and proximal duodenum.

Introduction

Amniotic fluid not only provides mechanical cushioning of the fetus but is also thought to be an important source of fetal nutrition and growth factors especially in the second half of pregnancy [1]. During this time the fetus swallows about 200-250ml/kg fetal weight/day. It has been estimated from animal studies that amniotic fluid provides 10-15% of the nutritional intake of the normal fetus in later pregnancy [2,3]. Low birth weight has been noted in infants born with various levels of digestive tract obstruction including oesophageal atresia [4,5], anorectal malformations [5] and duodenal atresia [6]. A study of infants with duodenal atresia, ileal atresia and colonic atresia suggested that infants with proximal atresia had lower birth weight than those with distal atresia [7].

These previous studies, other than Bacgi [4] have examined birth weight without adjusting for gestation at birth. Consequently the effects of atresia may have been overestimated. We aimed to investigate the relationship between level of congenital digestive tract obstruction and birth weight (BW) standard deviation score (Z-score) in an attempt to better understand the role of amniotic fluid in prenatal growth.

Methods

We performed a retrospective analysis of all admissions to a single neonatal surgical centre during the years January 1996 – March 2017 with congenital atresia of the digestive tract. Patient details were obtained from a prospectively maintained database. Birth weight, gestational age and gender of infants born with oesophageal atresia with or without tracheo-oesophageal fistula (OA), duodenal atresia (DA), jejunal atresia (JA) and ileal atresia (IA) were recorded and BW Z-scores calculated using LMSgrowth [8] using the British 1990 reference standard. Exclusion criteria included incomplete obstruction (stenosis), chromosomal or syndromic conditions, and multiple congenital malformations. Term infants (≥ 37 weeks completed gestation) admitted with suspected postnatal intestinal obstruction in whom no congenital malformation was found were used as a control group. The study was approved by our institution as a service evaluation.

Initially, we tested the null-hypothesis that there is no significant difference in birth-weight Z-score between infants born with a congenital atresia of the digestive tract and control infants. Birthweight Z-scores for infants born with each type of atresia were found to be normally distributed and therefore compared with control infants using a Students T-test. We then investigated the relationship between the level of congenital obstruction and birthweight Z-

score by comparing birthweight Z-scores for infants with congenital atresia beyond the stomach with infants with OA.

To investigate the relationship between gestational age at birth and degree of growth restriction we looked in more detail at infants with OA and DA, selected as the groups in whom there was significant growth restriction compared to controls. We compared birth weight z-score for infants born preterm (<37 weeks gestation) with those born at term (≥37 weeks gestation) with a T-test and then explored this relationship in more detail with linear regression analysis. Data are reported as mean±standard deviation (SD) and all analyses were performed using Prism v7.0 (GraphPad Software, CA).

Results

A total of 584 infants were identified and all were included. The number of infants in each diagnostic group is shown in Table 1.

Table 1: Number of infants in each diagnostic group

Diagnostic group	N
Control	293
Oesophageal atresia	148
Duodenal atresia	60
Jejunal atresia	26
Ileal atresia	57

Birthweight Z-scores for each diagnostic group with statistical comparison of each group against the control group is shown in Figure 1. For infants with OA and DA birthweight Z-score was statistically significantly lower than controls. However, birthweight Z-score for infants with more distal atresia (JA and IA) was similar to controls. Furthermore birthweight Z-scores for infants with OA were statistically significantly lower than infants with all more distal forms of congenital digestive tract atresia (Figure 1).

In infants born with OA, birth weight Z-score was significantly lower in infants born at term compared to those born preterm (mean -0.92±SD1.0 *vs* -0.48±0.87; p=0.01) and there was a significant negative correlation between BW Z-score and increasing gestational age (R^2 = 0.12; p<0.0001 Figure 2A). However birth weight Z-scores in infants born with DA were similar for term and preterm infants (-0.56±1.1 *vs* -0.23±1.4; p=0.3) and there was no significant correlation between birth weight Z-score and gestational age in DA infants (Figure 2B).

Discussion

Although the majority of fetal intrauterine nutrition is provided by the placenta there is evidence to suggest that a proportion of fetal growth in later pregnancy is achieved through absorption of components of amniotic fluid. Amniotic fluid is known to contain carbohydrates, proteins, hormones and growth factors [1]. In a rabbit model, ligation of the fetal rabbit oesophagus resulted in reduced fetal growth [9], a phenomenon reversed by gastric instillation of amniotic fluid but not by saline [3]. Reduced fetal organ and intestinal development have also been reported in similar animal models [3,10,11] and improvement in organ growth has been demonstrated following restoration of fetal swallowing [12].

The relationship between high obstruction of the digestive tract and low birth weight in human infants was recognised by Young in 1996 [6]. In 1969 Cozzi reported reduced birth weight in infants born with oesophageal atresia and anorectal malformations, the effect being more marked in the former [5]. He also reported a similar finding in infants with duodenal atresia which was more apparent in those with intrinsic rather than extrinsic obstruction and did not occur in more distal intestinal obstruction. More recently Bacgi [4] also demonstrated lower birth weight Z-scores in OA patients and noted that this was more marked in term compared to preterm OA infants. They surmised that this may indicate that the longer an infant with reduced amniotic nutrition remains in utero the greater the nutritional effect will be.

Our results confirm the findings by Bacgi [4] in showing a statistically significant difference in weight Z-score at birth between infants born with oesophageal atresia and controls. Our results show a similar effect in infants with duodenal atresia which is not seen in infants born with intestinal obstruction beyond the duodenum. Furthermore, infants with oesophageal atresia have significantly lower birthweight Z-score than those with duodenal atresia. These observations would fit with the concept that the prevention of absorption of amniotic fluid by high gastrointestinal obstruction in utero reduces fetal growth and that the effect is greater when the obstruction is more proximal. The difference seen between OA and DA suggests that significant absorption of nutritional and growth factors from amniotic fluid occurs in the stomach and proximal duodenum. Atresia beyond the duodenum, however, is not associated with significantly lower birthweight Z-score than controls suggesting that only a short length of small intestine is necessary for adequate amniotic fluid absorption to achieve satisfactory prenatal growth.

The relationship between BW Z-score and gestational age in infants with OA is almost identical to that demonstrated by Bacgi and colleagues [4]. This relationship demonstrates that the nutritional deficit in infants with OA becomes more marked with increasing gestation. This would support the concept that fetal growth related to ingestion of amniotic fluid, either due to nutrient or growth factor absorption, is of greatest importance during the latter stages of pregnancy. The absence of such a statistically significant relationship in infants with DA reinforces the concept that amniotic fluid is absorbed in the stomach and proximal duodenum; only complete pre-gastric obstruction characteristic of OA has the effect of limiting prenatal amniotic fluid dependent growth and this limitation appears to be related to gestational age.

The immediate clinical implications of the observed effects of reduced amniotic fluid absorption is that infants with OA and DA are born growth restricted and nutritionally compromised. They may therefore be at inherently increased risk of surgical complications and poor postnatal growth. A logical therapeutic approach would be to attempt to enhance growth in growth-restricted fetuses by the addition of nutrients to amniotic fluid. However this has not been successful [1] and trials of delivery of therapeutic agents to the fetus have had mixed results [13]. Infants with upper digestive tract atresia may also be at risk for poor growth during childhood and this may be in part a consequence of poor prenatal growth. Although there is a paucity of information on the growth in childhood of infants born with DA, children with OA have growth impairment at 5 years [14] but appear to have normalised by the age of 12 years [15]. In their analysis of growth of infants with OA up to 12 years of age, Vergouwe et al found that weight and height Z-score during childhood were significantly associated with birthweight. However, no analysis was performed for birthweight Z-score [15].

Due to the observational nature of this study it is possible that the observed effects are not solely due to anatomical location of digestive tract atresia but due in some way to other constitutional differences between these groups of infants. We acknowledge this as a potential limitation. In order to minimise the influence of other potentially confounding factors on our results we specifically excluded infants with chromosomal or syndromic conditions, and those with multiple congenital anomalies, all of whom may be more likely to have abnormal birthweight Z-score.

In conclusion, our data confirm that infants with proximal digestive tract obstruction are at risk of growth restriction, likely as a result of inadequate ingestion of amniotic fluid. The

knowledge that these infants are significantly growth restricted at birth should lead to closer observation of, and attention to, their postnatal nutrition and growth.

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Legends

Figure 1: Birthweight Z-scores by type of atresia.

Individual datapoints are shown with summary data as mean and SD. OA = Oesophageal atresia (with or without TOF), DA = Duodenal atresia, JA = Jejunal atresia, IA = Ileal atresia

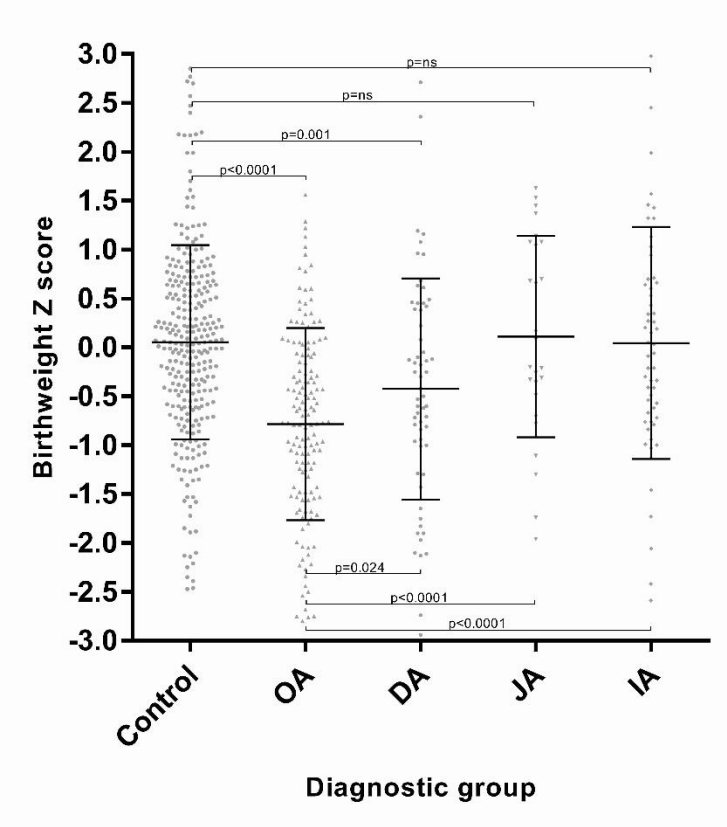

Figure 2: Relationship between gestational age at birth with birth weight Z-score in infants with (A) oesophageal atresia (n=148) and (B) duodenal atresia (n=60).