Case report: Goldenhar syndrome following donor oocyte IVF

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Abstract

Purpose To describe a case of Goldenhar syndrome in a couple receiving donated oocytes in an ‘egg sharing’ IVF cycle where the recipient of donor oocytes had Turner syndrome, hypothyroidism and gestational diabetes.

Methods Case report

Results Child born to oocyte recipient with Goldenhar syndrome

Conclusions We believe this is the first reported case of a child born with Goldenhar syndrome following use of donated oocytes in IVF by a woman with Turner syndrome, hypothyroidism and gestational diabetes.

Keywords Goldenhar · Oculo-auriculo-vertebral spectrum (OAVS) · Turner · Diabetes · IVF · oocyte-donation · Hypothyroidism

Introduction

Oculo-auriculo-vertebral spectrum (OAVS) or Goldenhar syndrome is a rare condition characterised by ocular, auricular and vertebral anomalies [1], that is estimated to occur in 1 in 5,600 newborn infants [2]. Although the aetiology of the condition is unknown, some familial cases with autosomal dominant or autosomal recessive inheri-

tance have been described. However Goldenhar Syndrome appears to be largely sporadic, has been reported in discordant monozygotic twins [3] and it has been suggested that such congenital anomalies are associated with assisted conception treatments such as In-Vitro Fertilisation (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI) [4, 5], bringing into question a genetic basis for the syndrome.

We present a case of Goldenhar Syndrome in a child born following an assisted conception cycle of oocyte ‘sharing’ IVF in which the oocyte recipient female had Turner syndrome, gestational diabetes and hypothyroidism.

Case Study

In October 2007 a couple were referred to our assisted conception unit following an unsuccessful vasectomy reversal in July 2006. Initial investigations on both partners were normal. The male partner underwent surgical sperm retrieval, motile sperm were successfully retrieved from the epididymis and frozen for use in subsequent Intra-Cytoplasmic Sperm Injection (ICSI).

The option of a ‘shared-egg’ treatment cycle was discussed and adopted by the couple as a method to help fund their own cycle of ICSI. (‘Egg sharing’ in the UK allows a woman to donate half of her oocytes in exchange for reduced cost treatment for herself and her partner). The female ‘sharer’s’ young age (25 years) together with her high level of Anti-Mullerian Hormone (AMH) (29.8pmol/L) and day 3 FSH level (8.5 iu/L) suggested that a large number of oocytes might be anticipated at oocyte collection and she was therefore accepted as an egg-sharer.

The couple with whom the oocytes were being shared (the ‘recipients’) had a diagnosis of primary ovarian failure and primary amenorrhea in the 45 year old female partner

Capsule We report a case of Goldenhar syndrome in a child born to a donor oocyte IVF recipient with Turner syndrome, hypothyroidism and gestational diabetes

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due to Turner Syndrome. The patient was characteristically short in stature with neck webbing. Investigations had, however, identified no cardiac malformations. The remaining X-chromosome exhibited a partial deletion of the long arm (13q). She also suffered from hypothyroidism. The male partner was 35 years of age with no history of illness or family history of genetic abnormality, his sperm function tests were normal. The couple received a previous donor oocyte IVF cycle in June 2007, from a different donor. A pregnancy was achieved but miscarried.

The ‘sharing’ woman underwent oocyte collection following standard ‘long protocol’ stimulation with depot GnRH agonist (Prostap SR 3.75 mg, Wyeth UK) beginning 3 weeks prior to 112.5iu daily urinary gonadotrophin (Menopur, Ferring UK) and hCG 5000iu (Pregnyl, Organon UK) after 14 days gonadotrophin stimulation. 12 oocytes were collected with ease and 6 were allocated to each couple. The oocyte ‘sharing’ couple underwent ICSI, 5 of the oocytes were mature and subsequently injected, 3 fertilised successfully and on day 3, two top grade embryos were transferred and the third frozen. The oocyte ‘recipient’ couple underwent standard IVF, all 6 oocytes were inseminated, 4 fertilised successfully and on day 3, two top grade embryos were transferred and the remaining two frozen. The ‘recipient’ endometrium was prepared using Oestradiol valerate (2 mg) 3 times a day for 8 weeks. Progesterone support (Cyclogest 400 mg, Actavis UK) was administered per vaginum 12 hourly for 6 weeks commencing on the day of the ‘sharers’ egg collection.

Two weeks post-embryo transfer a positive biochemical pregnancy was recorded for both couples. Ultrasound scans at 6 weeks revealed one fetal heart and an empty gestational sac in the oocyte ‘recipient’ couple but no fetal heart for the oocyte ‘sharer’.

During pregnancy the oocyte ‘recipient’ female took Thyroxine (25mcg daily) for hypothyroidism. She developed hypertension for which she received Methyldopa (250 mg tds) and gestational diabetes for which she received insulin (Novomix 30, Novo Nordisk).

The oocyte ‘recipient’ couple’s child was born, following emergency caesarean section at 30 weeks gestation due to preeclampsia, with noticeable facial abnormalities. The characteristics displayed in the child were a small dysplastic right ear, mild micrognathia (slight facial asymmetry) and thoracic hemivertebrae (T7 to T8 and T2 to T3), all consistent with Goldenhar Syndrome. In addition the child has since been diagnosed with plagiocephaly, atrial septal and apical ventricular defects. Chromosomal analysis was normal.

There was no apparent genetic history of the condition in the female ‘sharer’, however a decision was made that it was not appropriate for the couple to share their oocytes again due to the risk of another child being born

with Goldenhar Syndrome. Geneticists’ advice indicated a 2–3% risk of a subsequent child being born with the condition.

The oocyte ‘sharer’ couple subsequently received a second cycle of ICSI treatment, keeping all their oocytes. 26 were collected, 22 injected, 18 fertilised and on day 3, 2 top grade embryos were transferred and 14 frozen. Biochemical pregnancy was recorded two weeks post-transfer and an apparently healthy girl was born at 39 weeks gestation weighing 7lbs 10 oz.

Discussion

Goldenhar Syndrome is largely sporadic, but there have been reports of a genetic basis in some cases. Tasse *et al* [6] described the transmission of Goldenhar syndrome from a mother to her two daughters indicating autosomal dominant inheritance, additionally reporting patients who have inherited the condition in this way are more often bilaterally affected than patients where the occurrence is sporadic. Other reports have associated the syndrome with chromosomal abnormalities such as pericentric inversions of chromosome 1 [7] and 9 [8].

Some cases of Goldenhar syndrome have a genetic basis, however, this cannot be so for every case of the condition due to its highly sporadic occurrence and also reports of monozygotic twins of which only one twin has Goldenhar Syndrome [1, 3, 9]. Other explanations put forward to explain how the condition might arise include vascular disruption during morphogenesis in utero [3], gestational diabetes [10, 11] and assisted conception treatments involving ovarian stimulation [4, 5].

The patient ‘sharing’ her oocytes was found to have no obvious chromosomal abnormalities, with an apparently normal female karyotype. Family history to grandparents did not reveal any incidence of genetic or congenital abnormality.

The birth mother (the ‘recipient’ of the donated eggs) of the affected child was diagnosed with gestational diabetes. Goldenhar Syndrome has been reported in maternal diabetes [10, 11], however a link with gestational diabetes is unlikely as it occurs after organogenesis.

Egg donation in Turner syndrome was first described in 1984 [12] and is a well established practice [13]. There is some evidence that Turner syndrome patients have an altered uterine environment [14, 15]. However we found no evidence in the literature of a potential link between mothers with Turner syndrome and offspring with Goldenhar syndrome.

The negative implications of untreated hypothyroidism in pregnancy are well documented. Goldenhar syndrome in a child born to a hypothyroid woman has been docu-

mented on at least one occasion [16], but hypothyroidism is a common disorder and this does not provide any real evidence of a link.

Another explanation for the occurrence of Goldenhar Syndrome in this case could be Assisted Reproduction techniques such as IVF and ICSI themselves. Jongbloet [4] believed that there is a causal relationship between IVF and Goldenhar Syndrome due to the artificial nature of ovarian stimulation. ‘Overripeness Ovopathy’ as it was termed describes the development of a spectrum of preovulatory oocytes that are all in different phases of maturation when the Human Chorionic Gonadotrophin (hCG) dose is administered. The timing of this dose is optimal for some oocytes but too early or late for others that are less likely to develop normally and therefore could provide a plausible explanation for the link between infertility treatment and Goldenhar Syndrome. However, the numbers of reported cases of Goldenhar Syndrome after IVF or ICSI are quite low as reported by Yovich *et al* in response to Jongbloets paper, who could find only 1 case of Goldenhar from 450 infants delivered [5]. More recently Wieczorek *et al* [1] have concluded that infertility treatment is associated with an increased risk of Goldenhar Syndrome but state that the cause, whether from the controlled ovarian stimulation, in-vitro embryo culture and transfer or even the fertility diagnosis of the parents, is still far from clear.

Finally, the ‘recipient’ couple have 2 embryos remaining in storage from their treatment and have not yet indicated whether they wish to use the embryos in the future. The ethical and moral dilemmas posed by the use of embryos that might be genetically affected have been discussed by other authors [17] and are not small, but the risks in this case may be. Needless to say, the use of these embryos, if requested, will have to be carefully considered and may warrant ethics committee approval.

Conclusion

The cause in this complicated case remains elusive. Neither genetic nor environmental factors such as the IVF treatment itself can be ruled out completely. There is no evidence of a link between malformation and oocyte donation per se. However, the case may add some evidence to the ongoing debate on the relationship between Goldenhar syndrome and assisted conception treatment [1, 4, 5].

The evidence that the uterine environment might differ in women with Turner syndrome [14, 15] and the ‘recipient’s hypothyroidism [16] are worthy of discussion but suggestion of a causal link would be extremely speculative.

Nevertheless this first report of a child born with Goldenhar syndrome to a donor oocyte recipient with

Turner syndrome, hypothyroidism and gestational diabetes might add to the current poor understanding of the condition and its cause.

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