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REVIEW ARTICLE

Obstetric Complications of Donor Egg Conception Pregnancies

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Abstract
Ovum donation (OD) pregnancies are becoming increasingly common. Obstetric complications with IVF pregnancies are well documented. However, until recently OD had not previously been investigated as a separate subtype of this. It could be postulated that there may be more complications with OD pregnancies as the embryo is immunologically different to the mother. The subsequent allograft reactions can cause problems with placental development and function leading to pathology. Initial studies investigating OD pregnancies were inadequate due to small sample size and inappropriate control groups. Studies specifically comparing to spontaneous pregnancies alone are not suitable when we already know that IVF in itself increases the risk to both mother and baby. Recent research has optimised the control group by using women undergoing IVF with autologous ovum. Ovum donation has now been shown to be an independent risk factor for hypertensive disease in pregnancy, post-partum haemorrhage and increased risk of caesarean section. Neonatal outcomes are less clear-cut, although there is some evidence to suggest there is increased risk of small for gestational age babies and preterm delivery. It is now clear that OD pregnancies are higher risk than IVF pregnancies with autologous ovum and they should be treated as such. Women with ovum donation pregnancies should have obstetric-led care, in a unit which has ready access to both blood transfusion and cell salvage. Future research should investigate how to reduce the risk of ovum donation to these women.

Keywords Ovum donation · In vitro fertilisation · Pregnancy-induced hypertension · Pre-eclampsia · Post-partum haemorrhage · Surrogacy

Introduction

Ovum donation (OD) is a significant and important treatment option, not only for older women (as more than half of women aged over 45 years undergoing in vitro fertilisation (IVF) treatment will use donor oocytes), but also for younger women [1]. Reasons for women using donor ovum are many and include primary ovarian failure, surgical oophorectomy, after radiotherapy or chemotherapy, poor oocyte quality, multiple failures of IVF, genetic disorders, Turners syndrome and advanced maternal age [2]. Modern society where child bearing is delayed will only see this method becoming more prevalent.

Women who are donating eggs need be under 35 years of age (UK guidance), and they should ideally be between 23 and 30 years old. Older women should not donate eggs due to the increased risks of birth defects (such as Down's syndrome) and miscarriage. Eggs from older women may also affect pregnancy rates. It is a requirement for donors to have a BMI below 30 for their own safety. Donors are thoroughly screened prior to donation as per the UK good clinical practice advice. This includes karyotyping, virology screening, psychometric testing and detailed family history taking. It is important that donors are recruited carefully to ensure there are no adverse effects for the subsequent pregnancy.

It is now accepted that IVF treatment can increase the risk of obstetric complications such as hypertensive disorders, gestational diabetes (GDM), rate of caesarean section (CS), preterm delivery, post-partum haemorrhage (PPH), low birthweight and small for gestational age infants (SGA). What was less well known were the complications of specifically using donor ovum when compared to autologous

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ovum, as a subset of IVF pregnancies. Previously, studies were small and lacked appropriate control groups. This has now become a more frequently researched topic with appropriate control groups, and we now understand more about the outcomes of ovum donation pregnancies.

Although it is important to note the effect of maternal age on the outcomes of pregnancy; the majority of women having IVF and OD are older. Therefore, in this population it may be harder to differentiate whether the increased risks of GDM, hypertensive disorders, preterm labour and intrauterine growth restriction (IUGR) are due to the donor ovum, maternal age or a combination of the two [3].

Obstetric Complications

Hypertensive Disease

Hypertensive disease is the most common complication seen in pregnancies with OD. Rates of pregnancy-induced hypertension (PIH) and pre-eclampsia (PET) have been reported to range from 16 to 40% of women with OD, with PET specifically affecting 3–5% of all pregnancies [3].

It has been postulated that the increased risk in OD pregnancies may be attributable to immunological effects on the placenta causing pathology. Previous studies have shown that the rate of hypertensive disease is higher in those who had donor ovum from an unrelated person, compared to when the donor was a sibling [3].

A recent meta-analysis compared the rates of hypertensive disease in OD pregnancies compared to autologous IVF pregnancies and found that those who had OD were at significantly higher risk (nearly four times more likely to have hypertensive disease). Subgroup analysis also found this to be true in twin pregnancies when just analysing mothers over 40 years of age [3]. A further meta-analysis confirmed the increased rates of PIH and PET in OD pregnancies [4].

A national cohort study in Sweden found that both OD and IVF pregnancies with autologous ovum increased the risk of PIH and PET compared to those who conceived spontaneously (2.5 times higher for those with OD) [2]. A French study reported a statistically significant increase in PET rates in OD pregnancies when compared to both spontaneous conception and IVF without OD. PET rates were three times higher in OD pregnancies than those with spontaneous conception [5].

Twins have a statistically significant increase in both PIH (2.5 times higher) and PET (3.1 times higher) when comparing women with OD to those with autologous ovum [6].

It appears that the research unanimously agrees that OD increases risk of both PIH and PET and that this effect is not just due to maternal age. Women should be counselled specifically on the increased risk of PIH and PET prior to undergoing IVF and OD.

Gestational Diabetes

This was analysed in the meta-analysis by Jeve et al. [3], but the results were not statistically significant, although the rates of GDM were increased in those with OD pregnancy. No other study reviewed showed a significant increase in the rates of GDM with OD.

Small for Gestational Age

Meta-analysis of six studies demonstrated that the risk of an SGA infant was nearly two times more likely in OD pregnancies than autologous IVF pregnancies. However, the studies used for this had varying definitions of SGA, and there were no statistically significant differences in birthweight between these studies [3]. A further meta-analysis of 23 studies found that OD pregnancies are associated with a significantly increased risk of low and very low birthweight [7].

A small retrospective study noted that women with OD did not have a higher incidence of low-birthweight babies when compared to those with autologous IVF [8]. This mirrors other studies [9, 10] which demonstrate that those with OD were not at increased risk of IUGR, low Apgar scores, low birthweight when compared with controls. A national Swedish study found that those women with OD were found to be diagnosed with oligohydramnios more often compared to control groups. This was speculated to be due to the more frequent scans. This study also demonstrated no statistically significant differences in rates of SGA [2]. When looking at twins, there were no significant differences in birthweight or foetal growth restriction between groups [6].

The evidence for SGA appears to be a bit more mixed; however, on balance, there appears to be more in favour of no increased risk of SGA in OD pregnancies. In the UK, we currently do not routinely perform serial growth scans for women with IVF pregnancies with no other risk factors, and given the evidence, this seems appropriate. This should obviously be revised should the woman have any other risk factors for SGA or there are concerns about growth during pregnancy.

Intrauterine Death (IUD)

The rate of intrauterine death was analysed in the recent meta-analysis, and there was found to be an increased risk, although this was not statistically significant [3]. No other study reviewed specifically looked at this.

A study on twin pregnancies actually found that the risk of IUD was higher in those pregnancies that had not used IVF at all, likely due to the fact one in four was monochorionic and had been very preterm babies [6].

There are no meta-analyses reporting on early pregnancy loss or birth defects.

Preterm Delivery

Two recent meta-analyses reported that there was an increased risk of preterm delivery in OD pregnancies compared to autologous IVF pregnancies (nearly 1.5 times increased risk, with an incidence of 17%) [3, 4].

However, there are some studies that found no significant increased risk of preterm delivery in their population of OD pregnancies [2, 5].

Risk of CS

Meta-analysis by Jeve et al. [3] demonstrated that the risk of CS was increased nearly threefold in OD pregnancies compared to autologous IVF pregnancies, and this was mirrored by many other studies [4, 9, 10]. Both maternal age and multiple pregnancy were also noted to increase the rate of CS.

A national Swedish study also reported an increase in CS rate in those women with OD, although interestingly they noted that when compared to women who conceived spontaneously, women with OD pregnancies had more elective CS, whereas when compared to women undergoing IVF with autologous eggs, those with OD had a higher rate of emergency CS. It may be that this increase in elective procedures has more to do with the anxiety of the obstetrician with OD pregnancies than anything else. This study also demonstrated that CS was more frequent in women who had undergone IVF due to premature ovarian insufficiency or who were poor responders, compared to other indications for IVF [2].

All evidence reviewed suggests that CS is more common with OD. Haemoglobin should therefore be optimised antenatally, and women should be counselled appropriately in the antenatal period.

Post-partum Haemorrhage

Women having OD often already have many risk factors for PPH including multiple pregnancy, obesity, advanced maternal age and increased chance of requiring an operative delivery.

A small retrospective study comparing PPH > 500 ml in OD pregnancies with autologous IVF pregnancies found that the OD group had a statistically significant increase in rates of PPH (just over two times more likely). They also found that PPH was increased in the OD group compared to the autologous IVF group for nulliparous women, those with BMI > 25, aged between 41 and 45 year old, white ethnicity and surprisingly singleton pregnancies. Some of these subgroup results may be explained by the small sample size used. BMI and age are known to already increase risk of PPH; however, it is fair to say that OD would only increase this risk further [8].

Other studies confirm this increased risk in PPH (3.5 times increased risk, with an incidence of 4.2–17.3%) even after adjusting for possible confounding factors such as maternal age, parity, PET, type of pregnancy, mode of labour onset, mode of delivery and birthweight [2, 4, 6]. Studies also showed a statistically significant increased risk of blood transfusion and hysterectomies.

The evidence suggests that OD is an independent risk factor for PPH, and it should be treated as such. Women should have their haemoglobin optimised antenatally, have active third-stage management and deliver in a unit where there is access to blood transfusion, cell salvage and senior multidisciplinary team input.

Conclusion

Ovum donation is an effective method of artificial reproduction technique (ART) for women who are unable to utilise their own ovum for IVF. It is now more common with the rise in maternal age, and it is likely to become even more prevalent as time goes on. IVF pregnancies are known to be associated with increased risks for both mother and baby, and we now know that OD increases this risk further, specifically with regard to hypertensive disease in pregnancy, PPH and risk of CS. More data are needed on neonatal outcomes as there is currently conflicting evidence on SGA and preterm delivery.

These women should receive appropriate counselling about the increased risks of ovum donation pregnancies, preconception medical review and screening for pre-existing disease such as hypertension and diabetes prior to any fertility treatment. This discussion should also include advice regarding eSET (elective single embryo transfer) as multiple pregnancy increases the risk of preterm delivery. They should also have careful follow-up during the antenatal period and have obstetric-led care with input from a senior obstetrician. It is important to ensure that haemoglobin is optimised prior to delivery, whether that is with oral iron, iron transfusion or blood transfusion. Women should deliver in a unit with access to blood transfusion and cell salvage.

It is important to note that these risks also apply to surrogate pregnancies. Although women offering to be surrogates may be young and normally fit and well, the pathophysiology resulting from the immunologically different ovum may still occur and produce the same risks. Research comparing

gestational surrogates to spontaneous pregnancies reported a higher rate of both maternal (GDM, hypertension, use of amniocentesis, placenta praevia, antibiotic requirement during labour, and CS) and neonatal (preterm delivery, low birthweight) risks [11, 12]. Research also suggests that risks may be higher with fresh embryo transfer compared to frozen embryo transfer in this situation [13].

Future research is warranted into effective strategies to decrease the risks of OD pregnancies to both mother and baby antenatally, in labour, and postnatally. With the evidence demonstrating such increased risk of hypertensive disease in OD pregnancies, maybe OD should be considered a risk factor for starting aspirin antenatally. With this risk already well identified, research should maybe next look into whether aspirin can help reduce this risk. Another thought is whether uterine artery Dopplers would also be useful in this population to identify those more at risk of hypertensive disease in pregnancy. It also cannot be emphasised enough to these women the importance of maintaining good general health by not smoking, following recommended alcohol intake guidelines, maintaining a healthy weight and having regular blood pressure checks.

Also of note, there are no studies investigating the psychological impact of OD pregnancies. In order to provide holistic care for these patients, this would need to be rectified. Undergoing fertility treatment places a mental as well as physical strain on women, and to better understand this can only lead to better support and care for these women.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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