

A Comparison of Maternal and Neonatal Outcomes of 79 Ovum Donation Pregnancies Compared To 234 Autologous Ivf Controls

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Abstract

Objective: To assess complication rates for ovum donation (OD) pregnancies, including post-partum haemorrhage (PPH), pre-term delivery, and low birth weight, and compare these to autologous IVF controls.

Background: Ovum donation pregnancies have been shown to increase maternal and fetal risks including first trimester vaginal bleeding, pregnancy-induced hypertension (PIH), eclampsia, rate of caesarean section (CS), pre-term delivery, PPH, low birth weight and small for gestational age infants. The Homerton University Hospital has an onsite fertility unit which carries out approximately 100 ovum donation cycles per year and a tertiary maternity unit which delivers 6000 babies a year.

Methods: This is a retrospective analysis of 79 OD pregnancies and 234 autologous IVF controls who delivered between February 2011 and January 2015 at Homerton University Hospital. Data were collected using electronic patient records. Paired T-tests were used to determine significant differences between groups, and odds ratios used to determine significant differences between group outcomes.

Main Outcome Measures: Percentage of live births, method of delivery, incidence of PPH, and incidence of pre-term and low birth weight neonates.

Results: Our ovum donation population achieved a live birth rate of 98.7%. The majority (87%) of OD pregnancies were delivered by caesarean section (46% elective, 54% emergency), compared to 55% in the control group (45% elective, 55% emergency). Rates of PPH reached statistical significance ($P = 0.0097$) with PPH > 500 ml occurring in 82% of OD deliveries compared to 67% of control IVF deliveries. 29% of OD pregnancies had a PPH > 1000ml compared to 15% of control pregnancies. 28% of OD pregnancies were delivered preterm, and 36% were low birth weight (<2.5kg), but these were not significant when compared to controls.

Conclusion: Our study shows that OD pregnancies carry a higher risk than autologous IVF pregnancies for post-partum haemorrhage. Women should be counselled about this by fertility specialists prior to pregnancy.

They should be under consultant led care for their pregnancy and delivery. As OD pregnancies account for a relatively small number of IVF pregnancies, larger multi-centre studies are necessary to add to the data on this topic.

Keywords: Advanced maternal age, *in vitro* fertilisation, Ovum donation, Post-partum haemorrhage.

Abbreviations: OD: Ovum donation; PPH: Post-partum Haemorrhage; IVF: *in vitro* Fertilisation; CS: Caesarean Section.

Introduction

Ovum Donation

Ovum donation (OD) is becoming an increasingly significant fertility treatment option for advanced maternal age, primary ovarian failure, surgical oophorectomy, poor oocyte quality, multiple failures of IVF, and genetic disorders [1]. In a society

where the age of child bearing is becoming increasingly delayed, this method will only become more prevalent. It has been noted that over half of women aged over 45 who have undergone IVF have used donor oocytes, although numbers in younger women have also increased [2].

With advanced maternal age, a pregnancy is associated with increased risk of gestational diabetes (GDM), hypertensive disorders, pre-term labour, and intrauterine growth restrictions (IUGR) [3]. There is evidence that IVF treatment can also increase risk of hypertensive disorders, gestational diabetes, rate of caesarean section (CS), pre-term delivery, PPH, low birth weight and small for gestational age infants [4,5]. There is however limited data on ovum donation as a subset of this and whether this acts as an independent risk factor for post-partum haemorrhage. Recent meta-analysis has focused on hypertensive disorders and shown these to be more prevalent in OD pregnancies than autologous IVF pregnancies [3].

Post-partum haemorrhage

Post-partum haemorrhage is a leading cause of maternal morbidity and mortality, causing a quarter of all maternal deaths worldwide. In the UK, the risk of death from PPH is 1 in 100,000. The prevalence of PPH worldwide is 6%, and 1.86% for blood loss over 1L [6], although recent NHS maternity statistics reported a PPH rate of 13.8% [7]. At the Homerton, the rate of PPH loss of > 500ml is 38%, with the rate of PPH > 1500ml being 2.7%. For those having a caesarean section, PPH >500ml occurs in 26%. For the purpose of this study, PPH was classified as mild (500-1000ml), moderate (1001-1500ml) and major (>1500ml).

Morbidity associated with PPH can be significant including the need for blood transfusion, coagulation deficiencies, renal failure, and peri-partum hysterectomy [6].

Due to the magnitude of the sequelae of PPH, it is important that risk factors are identified antenatally and that appropriate intra-partum and post-partum plans are promptly implemented by the senior multi-disciplinary team if excess bleeding does occur. Women with ovum donation pregnancies often have multiple risk factors for post-partum haemorrhage such as multiple pregnancy, obesity advanced maternal age and increased chance of needing an operative delivery [8]. Our primary outcome measure was to compare incidence rates of PPH between OD and autologous IVF pregnancies in order to determine whether having ovum donation pregnancy in itself is a risk factor.

Methods

Using the Electronic Patient Records (EPR) system in place at Homerton, 79 OD pregnancies were found to be delivered between February 2011 and January 2015. These were matched for BMI and number of fetuses with 234 autologous IVF pregnancies delivered in the same time period. We were unable to match for age as autologous IVF pregnancies are very rare in advanced maternal age. Paired T-test statistics were used to analyse for any significant differences between the OD and control groups.

This was done using an online paired T-test calculator [9]. We utilised the EPR system to retrospectively collect data on these pregnancies, including demographics, past medical, surgical and obstetric history for the mother, details and complications of the pregnancy and delivery, and any complications for the neonate. The main outcome measures included percentage of live births, method of delivery, incidence of PPH, and incidence of pre-term and low birth weight neonates. Odds ratios as calculated by an odds ratio online calculator [10] were used to determine any statistically significant differences between the OD and control groups, with a significant P value being <0.05.

Results

Demographics

The average age for women having an ovum donation pregnancy was 43 years, compared to 37 years for autologous IVF pregnancies (Table 1). The majority of the patients in both groups were over 35 years old (88.6% in OD group and 67.5% in the control group). As expected a significant number (73 %) of women with ovum donation were over 40 years old compared to the control group (13.7%).

Characteristic	OD	Controls	P value	95% CI
Mean age (years)	42.38	36.94	<0.001	3.93 – 6.73
Mean BMI	25.85	25.38	0.1505	-0.39 – 2.47
Mean no. of fetuses	1.29	1.3	0.13	-0.01 – 0.26
Mean past parity	0.19	0.14	0.0004	0.09 – 0.29

Table 1: Characteristics of OD and control groups.

Despite national guidance on optimal BMI for those receiving fertility treatments, nearly half of women in both groups were overweight or obese. This equated to 49% of the OD group, and 47% of the control group with a BMI over 25, and 20% of the OD group and 11.5% of the control group with a BMI of more than 30. The vast majority of women were nulliparous and of white ethnicity. There was a comparably ethnically diverse population in both groups.

Post-partum haemorrhage

PPH >500 ml occurred in 82% of OD pregnancies compared to 67% of autologous IVF pregnancies, giving a statistically significant odds ratio of 2.32 (95% CI 1.23 – 4.39, P = 0.0097). The rate of PPH >500ml at Homerton over the same time period was 38%. PPH in the study was associated with caesarean section, advanced maternal age, and multiple pregnancies in both groups. However, it was significantly higher in the OD group than in the IVF group for nulliparous women, those with a BMI >25, of white ethnicity, aged between 41 and 45 years, and, surprisingly, with singleton pregnancies (Table 2).

Using our pre-defined categories, 75% of PPH in OD pregnancies were mild, 14% moderate, and 11% major, as compared to 78%, 13%, and 9% respectively in the control group (Figure 1). Analysing each category separately, mild PPH reached statistical significance (P = 0.0165), however moderate and major did not.

There were 3 cases of post-partum hysterectomy in the OD group (3.8%) and 1 case in the control group (0.4%).

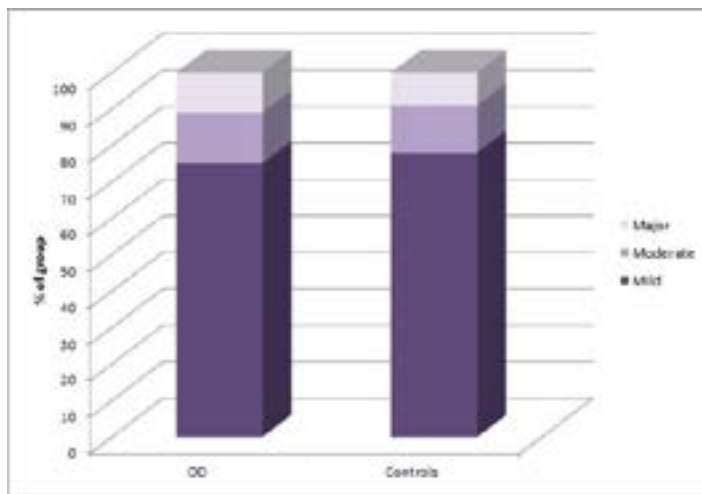


Figure 1: Categories of PPH in OD and Control groups.

		OD % (no) N = 65	Controls % (no) N = 156	Odds ratio	P value
No. of fetuses	Singleton	79 (46)	60 (101)	2.54	0.01
	Twin	89 (17)	84 (52)	1.16	0.55
	Triplet	100 (2)	75 (3)	2.14	0.68
Age (years)	26 - 30	2 (1)	4 (7)	1.40	0.84
	31 - 35	9 (6)	28 (44)	1.50	0.64
	36 - 40	17 (11)	56 (87)	4.93	0.13
	41 - 45	48 (31)	10 (15)	4.48	0.01
	46 - 50	23 (15)	2 (3)	1.25	0.86
	>50	2 (1)	0 (0)	7.67	0.35
Previous Parity	0	85 (56)	67 (138)	3.07	0.004
	1	64 (7)	65 (15)	1.24	0.79
	2	100 (2)	60 (3)	3.51	0.47
BMI	<= 25	49 (32)	50 (78)	2.05	0.09
	>25	51 (33)	50 (78)	2.79	0.05
Ethnicity	Asian	9 (6)	11 (17)	2.12	0.52
	Black	14 (9)	15 (23)	3.13	0.31
	Oriental	2 (1)	0.6 (1)	1.0	1.0
	White	75 (49)	73 (114)	2.22	0.03
	Mixed	0 (0)	0.6 (1)	3.0	0.67
	Not known	0 (0)	0 (0)	0.3	0.67
Mode of delivery	SVD	3 (2)	10 (15)	1.04	0.96
	Instrumental	3 (2)	17 (26)	1.92	0.60
	Elective CS	43 (28)	33 (52)	0.67	0.58
	Emergency CS	51 (33)	40 (62)	1.20	0.78
	Total CS	94 (61)	73 (114)	0.94	0.89

Table 2: Characteristics of OD and Control pregnancies with PPH >500ml.

Neonatal outcomes

Nearly all (99%) women pregnant with ovum donation pregnancies had a live birth. A quarter of women in both groups delivered twins. There were 2 women with ovum donation pregnancies who delivered triplets and 4 women in the control group.

In both groups approximately a quarter of women delivered before 37 weeks (28% in OD group, and 24% in the control group). Approximately a third of both groups had low birth weight neonates <2500g (36% in the OD group, and 30% in the control group).

Discussion

In ovum donation pregnancies, when compared to a control group with autologous IVF pregnancies, women have a statistically significantly higher rate of PPH >500ml (82% compared to 67%). PPH was also significant in the OD group compared to controls if the mother was aged between 41 and 45 years, if she had a BMI of >25, if it was a singleton pregnancy, if she was white, or if she was nulliparous. This indicates that women undergoing IVF with OD should be counselled antenatally about the increased risk of PPH, especially if she has any of the aforementioned characteristics.

Women over the age of 40 years have poor ART success when using their own oocytes when compared to those using donor oocytes [11]. These older reproductive age group women are more likely to be counselled to use donor oocytes. This skew in groups would likely be representative of the population seeking fertility treatment. PPH was significant in the OD group when the mother was aged between 41 and 45 years. Research by Krieg et al. found no difference in maternal and neonatal outcomes when comparing to autologous IVF pregnancies with advanced maternal age. They suggested that previously described differences in outcomes between OD and IVF groups would be because of the increased risks of the advanced age of the OD group.

Caesarean section (CS) is known to be a risk factor for PPH, with an incidence of PPH in CS between 3-10% [12]. One study documented an incidence of PPH >1000ml of 4.84% in elective CS and 6.75% in emergency procedures [13]. The total CS rate at the Homerton is 30%. Risk factors for PPH after CS include previously retained placenta, clotting disorders, preterm birth, general anaesthesia, fibroids, adherent placentation, and antepartum bleeding. 94% of OD PPH women had undergone CS compared to 73% of control PPH women. Although the absolute percentages appear quite different, this did not reach statistical significance. This suggests that we cannot attribute the increased rate of PPH in OD women to having had a CS.

Our data suggest that PPH occurred more in OD singleton pregnancies than control singleton pregnancies. PPH was also significantly higher in those who were having their first baby. It is known that multiple pregnancies are a risk factor for PPH [14], but we did not demonstrate a significant difference in PPH between groups with multiple pregnancies. This could be attributed to the small numbers in our study.

We also found that OD mothers of white ethnicity had a higher incidence of PPH compared to controls. There were no differences between other ethnicities. It has been documented that women of Hispanic and Asian ethnicity may be more at risk of atonic uterus and as a result PPH [14], although we did not find this. This again could be due to small numbers, as the majority of both of our groups identified as ethnically white.

It is known that obesity is associated with negative outcomes in obstetrics [15], regardless of method of conception, perhaps due to derangement of the HPO axis, oocyte quality, and receptivity of the endometrium. Studies have shown that obese women who lose at least 10% of their body weight have better pregnancy outcomes than those who do not [15,16]. Obesity is associated with many complications including thromboembolism, hypertension, gestational diabetes, congenital malformations, macrosomia, subsequent obesity of the child, infertility, miscarriage, delivery and surgical complications (including increased likelihood of instrumental delivery and CS and anaesthetic difficulty). 7.2% of women delivering at Homerton have BMI >35. The risk of PPH rises with BMI, being more frequent in 30% of women with a moderately raised BMI, and 70% of those with a highly raised BMI [18,19]. Our data show that in women with a BMI over 25, the incidence of PPH was significantly higher in OD pregnancies compared to controls. There was no difference in PPH between groups in women with a healthy BMI. This suggests that if a woman is overweight, ovum donation can then further increase her risk of PPH.

Ovum donation pregnancies were not shown in our study to have a higher number of babies with low birth weight compared to IVF control group. This mirrors other studies which also have found no difference [1]. This could suggest that ovum donation does not carry increased neonatal risks compared to autologous IVF, but this would need much larger number to allow detailed analysis. Our data also did not show a correlation between gestation at delivery and postpartum haemorrhage.

A limitation of this study is the small numbers of women with ovum donation pregnancies. However the strength of our study is that all women were looked after and delivered by the same group of clinicians working on one site, and supported by the same level 3 neonatal intensive care unit. Meta-analyses or multi-centre studies would be helpful in combining data on this still rare fertility treatment, to elucidate outcomes and support women and their families to make informed choices.

Another limitation is the increased age in the OD pregnancy group; this meant we were unable to match the groups for age. We used, as far as was possible, an appropriate control group; by using autologous IVF pregnancies as a control group, this removed the increased risk and complications associated with IVF when compared to spontaneous conception pregnancies (although it is uncertain whether this increased risk is due to the procedure itself or due to the condition of infertility). We also matched the groups as closely as possible to remove confounding factors that would

change a woman's risk, such as increased BMI. Although we have demonstrated that OD pregnancies have a significantly higher incidence of PPH, we cannot completely exclude the effect of age and we are not sure this would ever be possible due to the natural limitation of age on a woman's reproductive potential.

Conclusion

Ovum donation pregnancies have been shown to have increased risks over autologous IVF pregnancies, and are likely to become more common as maternal age advances in line with modern living and lifestyle. We have demonstrated that women with ovum donation had a significantly higher rate of PPH compared to autologous IVF controls. The underlying mechanism for this can be postulated to be immunological, although it is not yet fully defined. Based on our findings, it could be suggested to antenatally counsel women with ovum donation regarding the risk of PPH. Women should be encouraged to book at hospitals with good access to multidisciplinary teams and special care baby units and who can treat women with PPH. Women should have antenatal optimisation of haemoglobin, obstetrician led care for delivery in a centre with access to cell salvage and prompt availability of cross-matched blood and blood products. Continued research, ideally a larger multi-centre study, is needed in this area to further define the risks to women undergoing OD, as current numbers in the literature are small. This will help fertility clinicians and obstetricians to appropriately advise and manage these women throughout their pregnancy, labour, and puerperium.

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