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ASSISTED REPRODUCTION

In vitro fertilisation (IVF) with donor eggs in post-menopausal women: are there differences in pregnancy outcomes in women with premature ovarian failure (POF) compared with women with physiological age-related menopause?

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Abstract
Purpose This study assessed pregnancy rates and obstetric outcomes in women with premature ovarian failure (Group A) with post-menopausal women ≥40 years (Group B) who had IVF ± ICSI using donor eggs.
Methods This was a retrospective analysis of 54 recipients with either premature ovarian failure or physiological menopause undergoing oocyte donation between 2000 and 2007 at Monash IVF.
Results The average number of stimulated cycles required for a woman in group A and B to deliver a baby was 1.75 and 1.4 respectively. Both groups had high cumulative pregnancy rates; however, there was a statistically significant difference with regards to rates of complications.
Conclusion Oocyte donation in both premature ovarian failure and physiological menopause is highly successful and cumulative pregnancy rate is an important statistic which can be used to inform women seeking this technique. High rates of complications, in conjunction with individual risk-factor analysis needs to be considered when counselling post-menopausal women about oocyte donation.

Keywords Cumulative pregnancy rate · Oocyte donation · Outcomes · Post-menopausal · Premature ovarian failure

Capsule Oocyte donation in POF and physiological menopause is highly successful. However, there are significant differences in rates of complications between these two groups.

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Introduction

For over 20 years oocyte donation and IVF has been used as an aid for conception for young women with premature ovarian failure (POF). Currently, it is also being used increasingly to overcome the age-related decline in fertility [1, 2]. In Australia and New Zealand in 2005, 894 cycles of IVF were initiated for oocyte donation, representing approximately 3% of the total IVF ± ICSI treatment cycles, compared with just 391 cycles in 1994 [3].

POF is the cessation of ovarian function before the age of 40 yrs, and effects 1% of women [4, 5]. It is characterized by amenorrhea, either primary or secondary, and symptoms of hypoestrogenism, with elevated serum gonadotropin concentrations. The aetiology of POF is diverse and includes chromosomal, autoimmune, iatrogenic, infectious, and idiopathic causes [6].

Age appropriate menopause is defined as menopause occurring after the age of 40 years. The postponement of childbearing and the success rates of oocyte donation seen

in post menopausal women have contributed to the rise in initiated cycles over recent years [1].

Many studies have depicted comparable rates of pregnancies amongst young and older women using donor eggs [1, 7]. One of the principal concerns regarding this process is the incidence of obstetric and neonatal complications that may arise in the older age group. Our study was undertaken to assess both pregnancy rates (PR) and obstetric outcomes in women with POF (Group A) with post-menopausal women ≥40 years (Group B) who had IVF ± ICSI using donor eggs at Monash IVF.

Materials and methods

This was a retrospective analysis of 54 recipients with either POF or physiological menopause undergoing oocyte donation between 2000 and 2007 at Monash IVF. The majority of women who undergo egg donation are either peri-menopausal or have low ovarian reserve. As per our definition and strict inclusion criteria, we have only included women who were post-menopausal in this study. All recipients were placed into one of two groups according to their indications for oocyte donation. There were 36 women in Group A (POF group) with an average age of 28.3 years (±6.1) and 18 women in Group B (post-menopausal group; ≥40 yrs) with an average age of 45.6 years (±3.4). Menopause (either POF or physiological) was defined as amenorrhoea for greater than 12 months duration with two FSH concentrations >20 IU/L. Women who used donor eggs for poor ovarian reserve and were still menstruating were excluded.

Donor oocyte retrievals were performed 38 h post human chorionic gonadotrophin (hCG) administration (either recombinant [rhCG] Ovidrel (Merck Serono Australia) at 250 μg or urinary [uhCG] Pregnyl (Organon Australia) at 10,000 IU). Oocytes were fertilised using either standard insemination or ICSI and fertilisation results assessed between 16–20 h post sperm insemination. Embryos were transferred (ET) between day 2 to 5 with no more than two embryos being transferred at any one time. Patients may elect to have one or two embryos transferred or alternatively patients may only have one or two embryos available for transfer with no other embryos available. Luteal support consisted of either Crinone (Merck Serono Australia) or Progesterone Pessaries (Orion Australia).

Clinical pregnancy was defined as the presence of at least one gestational sac on ultrasound in the first trimester. Implantation rate was the number of foetal heartbeats on ultrasound divided by the number of embryos transferred in the corresponding cycle. Ongoing pregnancy was a pregnancy beyond 20 weeks gestation and a completed pregnancy a delivery beyond 20 weeks gestation whether that resulted in a live birth or a still birth. Cumulative pregnancy rate (CPR) was the overall chance of achieving a pregnancy.

Paired χ^2 analysis was used to ascertain statistical differences using a Minitab® package (Minitab version 7.3).

Results

In this study the potential difference in pregnancy rate (PR) between standard IVF and ICSI were examined, however as it was found that there was no significant difference, both standard IVF and ICSI were grouped together for analysis. We did not examine perinatal outcomes that could potentially be influenced by the method of insemination.

A total of 95 cycles were initiated via stimulation with a subsequent 88 ET procedures from these cycles. Initiated cycles refer to ovarian stimulation in the donor, who then donates the retrieved oocytes to another woman where they are inseminated either by standard IVF or ICSI; some embryos were transferred (maximum of two) and suitable supernumerary embryos cryopreserved for potential future use. Comparison between the groups, in both fresh and frozen embryo cycles is presented in Table 1.

In group A, a total of 134 cycles were initiated, 70 of these were fresh cycles with 55 embryo transfer procedures, and 64 initiated frozen cycles with 58 embryo transfer procedures. In group B, a total of 44 cycles were initiated, 25 fresh with 23 transfer procedures, and 19 initiated frozen cycles with 18 embryo transfer procedures. The implantation rate as a percentage of embryos transferred was not

Table 1 Comparison of fresh versus frozen embryo transfers

	Fresh		FET	
	Group A (Age<40years) *n*=36	Group B (Age≥40) *n*=18	Group A (Age<40years) *n*=36	Group B (Age≥40) *n*=18
Initiated cycles	70	25	64	19
Cycles w Embryo transfers	55	23	58	18
Ongoing pregnancies	15	12	19	5
Implantation rate (%)	19	32	20.5	16

statistically different between Groups A and B in either the fresh (p=0.067) or frozen embryo transfers (p=0.312).

Cumulative PRs were 75% for Group A and 72% for Group B, with no significant difference between the two groups. The average number of stimulated cycles for each woman to produce a live birth was 1.75 and 1.4 for group A and B respectively.

Major or minor complications occurred in 27 women. A total of 12 out of the 40 pregnancies in Group A (30%), compared to 15 out of 18 (83%) total pregnancies in group B. The rate of complications between the two groups was significant (p=0.001). Table 2 lists the obstetric and neonatal problems encountered, which included pre-term labour, gestational hypertension, gestational diabetes mellitus (GDM), premature rupture of membranes (PROM), placental complications and intrauterine growth retardation (IUGR). There were no maternal or neonatal deaths. The chromosomal abnormality identified as a trisomy 21, whereby the donor's age was under the age of 35 and the semen parameters were within the normal range.

Forty five percent of the cycles in Group A were single embryo transfers, compared to 38% in Group B. Of all the cycles that resulted in pregnancy, there were three pairs of twins in total. Two of these were from a 2-embryo transfer on day 3 (both of the recipients were under 40 yrs), and the third was from a 2-embryo transfer in a recipient over the age of 40 yrs who subsequently developed GDM.

Discussion

Oocyte donation represents a unique opportunity in the treatment of infertility. In our institution, we have been performing egg donation since 1982. As with conventional IVF, our techniques and methods are constantly evolving as can be seen in the trend towards fewer numbers of embryos being transferred during a cycle [3]. Smaller numbers of embryos transferred have been shown to provide optimal implantation rates with least chance of multiple gestations and hence less pregnancy-related complications [1, 7, 8]. In our study, in keeping with the recommendations of the Fertility Society of Australia [9], the average number of embryos transferred per cycle in both age groups was 1.5.

Table 2 Analysis of complications between the two groups

	Group A (Age<40years) n=36 *Pregnancies= 40*	Group B (Age≥40) n=18 *Pregnancies= 18*
Pre-term labour	3	5
Gestational Hypertension/ Preeclampsia	5	3
GDM	2	2
PROM	1	1
Placental complications	0	1
IUGR	1	2
Chromosomal	0	1
Deaths	0	0

There have been conflicting results published regarding the success of oocyte donation in different age groups [10–12]. Whilst some studies have not detected any difference [1, 11, 13], others have depicted decreased rates of pregnancy and increased pregnancy-related complications in women over the age of 40 yrs [14–16].

Few studies specifically compare post-menopausal women to younger women with POF [17–19]. Among the two groups of women who received donor eggs, this study demonstrates that overall success rates (as judged by implantation and clinical pregnancy rates) are comparable between the groups with no significant differences demonstrable, regardless of age or aetiology. These findings are consistent with similarly conducted previous studies [17–19]. However, this study does in fact demonstrate significantly higher rates of complications in the older menopausal group; 80% experienced minor or major complications in the menopausal group compared to just 30% in the younger group. . Even though we can overcome implantation failure in the older menopausal group we are unable to overcome the higher rates of complications that have previously been shown in other studies.

A recent publication by Soares et al, depicted significantly lower PR and higher miscarriage rates when women were grouped into <45 yrs and ≥45 yrs in oocyte donation cycles [18]. Although there are conflicting results, based on age, generally studies tend to depict favourable outcomes in all age groups, regardless of aetiology, up to the age of 45 years. As women approach and exceed 50 yrs of age, complications such as increased hospitalisation, pregnancy-induced hypertension, GDM and lower birth-weight babies begin to surface [14, 18, 19].

In our study implantation rates and ongoing PRs were not significantly different between women with POF versus post-menopausal women in either the fresh or frozen ETs. Although past studies have depicted a significantly lower implantation rate in cryopreserved ET cycles [12], this study demonstrates no difference thus limiting the number of stimulated cycles with oocyte retrieval required for donors. In our study the majority of older patients underwent ICSI cycles. The low number of recipients due to our strict inclusion criteria makes it impossible to compare ICSI versus standard IVF.

In this study the average number of stimulated cycles required for a woman in group A and B to deliver a baby was 1.75 and 1.4 respectively. This, combined with a

cumulative pregnancy rate (CPR) of 75% in group A and 72% in group B, is encouraging for both groups of women seeking oocyte donation. Few studies comment on CPRs but rather report clinical PR and rates of delivery [1, 13, 19]. CPRs provide an important guide for overall success of delivering a baby for women seeking oocyte donation. Reported CPRs have increased over the years [1]. In a more recent study by Budak et al, CPRs of 87% and 96.7% after three and five attempts respectively were reported [1] in a group of patients. Our CPRs are comparable with such studies given that our average number of embryos transferred is a low 1.5. These values provide promising information for women, regardless of indication for oocyte donation.

Conclusion

In summary, this study demonstrates that IVF ± ICSI using oocyte donation, whether fresh or frozen embryos are transferred is highly successful. Cumulative pregnancy rate and number of stimulated cycles required for pregnancy are important and relevant statistics which can be used to inform women seeking pregnancy via IVF and egg donation. Although it is reassuring to postmenopausal women that their chances of conceiving and having a baby are excellent, it is important they understand the much higher rates of minor and major complications involved when conceiving a baby at this stage. Therefore, information regarding complications in pregnancy needs to be considered in conjunction with individual risk-factor analysis when counselling older post-menopausal women.

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