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Review article

Higher risk of preterm birth and low birth weight following oocyte donation: A systematic review and meta-analysis

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ABSTRACT

Objectives: To perform a systematic review and meta-analysis of the known literature to assess whether the perinatal outcomes are different after oocyte donation (OD) compared to autologous oocyte (AO) in vitro fertilization (IVF) pregnancies.
Study design: A systematic literature search was done for studies published in English from 1980 to 2016. Studies comparing perinatal outcomes of pregnancies following fresh or frozen OD and AO IVF were included. Meta-analysis was performed using the Rev Man 5.3 software (Cochrane Collaboration) for the perinatal outcomes of PTB (<37 weeks), early PTB (<32 weeks), LBW (<2500 g), very LBW (<1500 g), and SGA (<10th centile). Six studies provided data on PTB, three studies on early PTB, five studies on LBW, four studies on very LBW and three studies on SGA after fresh embryo transfer. Two studies provided data on PTB, early PTB, LBW and very LBW after frozen embryo transfer.
Results: There is an increased risk of PTB following fresh embryo transfer in OD pregnancies than in AO IVF pregnancies (OR 1.45, 95% CI 1.20–1.77). If the PTB risk is assumed to be to 9% for pregnancies following AO IVF, then OD pregnancies will have a PTB risk between 10.8% and 15.9%. Similarly, the risk of LBW is higher after fresh embryo transfer in OD pregnancies than AO IVF pregnancies (OR 1.34, 95% CI 1.12–1.60). If the assumed LBW risk is 9% for AO IVF pregnancies, then OD pregnancies have a LBW risk between 10.1% and 14.4%. There is an increased risk of early PTB (OR 2.14, 95% CI 1.40–3.25) and very LBW (OR 1.51, 95% CI 1.17–1.95) in a fresh embryo transfer after OD as compared to AO IVF pregnancies.
Conclusions: There appears to be a higher risk of adverse perinatal outcomes following fresh OD compared to AO IVF pregnancies.

Contents

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Introduction

The average age at first childbirth has been steadily increasing over the last few decades. Birth data from the registries of European countries and the United States indicates that the average age at first childbirth has been steadily increasing across countries from 25.6 years in 1970 to 29.4 years in 2008 [1]. This trend is reflected in the increasing average age of women undergoing *in vitro* fertilisation (IVF) [2]. An important predictor of a live birth following an IVF cycle is maternal age [3], and improvements in IVF techniques have proven insufficient to compensate for the decline in fertility with increasing maternal age [4]. Although there is widespread interest and research in the prospect of reversing this age-related decline in IVF success, most of these methods such as androgen supplementation for poor responders, mild stimulation protocols and pre-implantation genetic screening [5–7] have not been yet proven to be effective. In the last decade, oocyte cryopreservation in anticipation of age-related fertility decline has been suggested as a preventative measure, but this not only brings on its own ethical issues but also requires that oocyte preservation is done at a younger age in anticipation of future fertility decline. This requires significant forethought and planning and a recent study suggested that the optimal age for egg freezing in anticipation of age-related infertility is around 37 years, and egg freezing beyond this age would not be cost-effective due to declining success rates [8]. In addition, there is a lack of long-term safety data for oocyte preservation and it is unclear as to the number of oocytes that need to be frozen to give a reliable 'guarantee' to guard against future fertility decline [9].

Oocyte donation (OD) is currently the most successful fertility treatment option for women with age >40 years and diminished ovarian reserve with live birth rates between 30- 40% [10]. In addition, it is the only method of fertility treatment in women with primary ovarian insufficiency which could be due to previous gonadotoxic therapy, genetic conditions (such as Turner's syndrome and Fragile X syndrome) or secondary to autoimmune conditions. The live birth rates following OD treatment primarily depends on the age of the donor and is independent of the age of the recipient [11].

Obstetric complications, such as hypertensive disorders and gestational diabetes increase with advancing maternal age and these risks are primarily influenced by the oocyte recipient's age and pre-conceptional health rather than the oocyte source [12,13]. Around 60% of women who were recipients of OD cycles across Europe in 2012 were older than 40 years [10]. Due to this reason alone, the majority of OD pregnancies are considered high risk. Apart from age factor, infertility and IVF treatment have been associated with adverse perinatal outcomes compared to natural conceptions even in singleton pregnancies [14].

Furthermore, there have been reports in the literature that there is an increased risk of adverse obstetric and perinatal outcomes with OD than autologous oocyte (AO) IVF cycles even when controlling for the age of the recipient [15]. There have been suggestions that an immune intolerance between the recipient's endometrial interface and the oocyte from a donor may mediate an increased risk of abnormal placentation [16]. However, the evidence is conflicting with some studies suggesting an increased risk of adverse perinatal outcomes with OD pregnancies [17,18] with others finding no difference [19,20]. Due to the ambiguity in literature, we decided to perform a systematic review of the available literature and synthesise the data from studies comparing perinatal outcome data between OD and AO IVF pregnancies.

Materials and methods

A systematic search of the literature was performed to identify studies which compared perinatal outcomes following OD versus AO IVF pregnancies. Only studies which had separately reported on the outcome of fresh and frozen embryo transfers following OD and AO IVF cycles were included. As there is evidence that the perinatal outcomes of birth weight and gestational age vary between fresh and frozen embryo transfers [21], we planned to compare the outcomes of fresh OD and AO IVF pregnancies separate from frozen OD and AO IVF pregnancies. We excluded studies which included both fresh and frozen cycles but did not report fresh and frozen cycle data separately. The analysis was restricted to singleton births. The outcomes assessed were preterm birth (PTB), early preterm birth (early PTB), low birth weight (LBW), very low birth weight (very LBW), small for gestational age (SGA), congenital anomalies and admission of the neonate to intensive care. PTB and early PTB were defined as a live birth before 37 weeks and 32 weeks respectively. LBW and very LBW were defined as birth weight lower than 2500 g and 1500 g respectively [22]. SGA was defined as a birth weight less than 10th centile for that gestational age [23].

The search was limited to studies published in the English language from 1980 to December 2016. 1980 was taken as the limit for systematic search as the earliest reported pregnancy in the literature from a donated oocyte was reported in 1983 [24] and the first live birth in 1984 [25]. Electronic databases: MEDLINE, EMBASE, and Web of Science were searched from the year 1980 until December 2016 using keywords "Donor oocyte AND (autologous OR own) oocyte" in addition to hand-searching of the reference list of the included studies. Two authors (MM & MSK) independently identified the potential titles and abstracts for eligible studies. In the case of any ambiguity about a study; the full text was obtained to get additional information about inclusion and exclusion criteria. The selection process was reported in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. A predefined data extraction form was independently filled by two authors (MM & MSK) from the eligible studies and any disagreements were resolved by discussion with a third author (SKS). The data synthesis and analysis was done using the Rev Man 5.3 software (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration; 2014.). The I^2 statistic was used to assess the impact of heterogeneity on the meta-analysis. An $I^2 > 50\%$ indicated moderate heterogeneity and >75% indicated high level of heterogeneity. In case of high heterogeneity; we looked for obvious clinical heterogeneity among pooled studies. If no such clinical heterogeneity was found; we used random-effects model. The quality of the included studies was assessed using the critical appraisal skills programme (CASP) checklist for cohort studies [26].