REVIEW

A meta-analysis of neonatal health outcomes from oocyte donation

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Donated oocytes are a treatment modality for female infertility which is also associated with increased risks of preeclampsia. Subsequently it is important to evaluate if there is concomitant increased risks for adverse neonatal events in donated oocyte neonates. A structured search of the literature using PubMed, EMBASE and Cochrane Reviews was performed to investigate the perinatal health outcomes of offspring conceived from donor oocytes compared with autologous oocytes. Meta-analysis was performed on comparable outcomes data. Twenty-eight studies were eligible and included in the review, and of these, 23 were included in a meta-analysis. Donor oocyte neonates are at increased risk of being born with low birth weight (<2500 g) [risk ratio (RR): 1.18, 95% confidence interval (CI): 1.14–1.22, P-value (P) < 0.00001], very low birth weight (<1500 g) (RR: 1.24, CI: 1.15–1.35, P < 0.00001), preterm (<37 weeks) (RR: 1.26, CI: 1.23–1.30, P < 0.00001), of lower gestational age (mean difference −0.3 weeks, CI: −0.35 weeks to −0.25 weeks, P < 0.00001), and preterm with low birth weight (RR: 1.24, CI: 1.19–1.29, P < 0.00001), when compared with autologous oocyte neonates. Conversely, low birth weight outcomes were improved in term donor oocyte neonates (RR: 0.86, CI: 0.8–0.93, P = 0.0003). These negative outcomes remained significant when controlling for multiple deliveries. The donor oocyte risk rates are higher than those found in general ART outcomes, are important considerations for the counselling of infertile patients and may also influence the long term health of the offspring.

Introduction

The use of donor oocytes is an increasingly common strategy for the treatment of female infertility. The manipulation of gametes and culture of embryos, however, have the potential to negatively influence embryological development and perinatal outcomes compared to normally conceived children.[1] Moreover, Assisted Reproductive Technologies (ART) perinatal outcomes are worse than those observed from spontaneous conceptions with increased incidences of birth defects (BD), preterm delivery (PD), lower birth weights and mortality.[2–7] Additionally, poor neonatal outcomes have been linked with increased incidences of morbidity and mortality in later life in the general population,[8–10] and phenotypically normal ART offspring have also been linked to increased epigenetic changes throughout their genome.[11]

With adverse perinatal outcomes from the ART population already established, there is an opportunity to consider the pattern of outcomes within specific exposure groups to identify opportunities for intervention and to inform patient decision making. Donor oocyte conceptions form one such sub-group and has a novel characteristic within the ART population. The woman receiving treatment will be gestating an embryo derived from another woman's oocyte which potentially represents an immunological challenge to the mother.

The incidence of preeclampsia is increased when donated oocytes are used in infertility treatments.[12–14] Preeclampsia is argued to be an immune response[15,16] that can alter placentation[17,18] and is a leading cause of foetal and maternal morbidity and mortality.[19] Notably, the immune mechanism of preeclampsia is associated with factors such as intra uterine growth retardation (IUGR) and PD known to adversely affect the health of the child.[20,21] Individuals born following preeclampsia in their gestation have an increased risk of hypertension,[22–24] endothelial dysfunction,[25] higher body mass index (BMI),[26] epilepsy,[27] increased hospitalization due to disease,[28] and stroke.[29] Preeclampsia has also been associated with an increased risk of an autism spectrum disorder in offspring.[30] Millis found that the placenta suffered from altered methylation due to preeclampsia and that infants also had altered methylation of insulin-like growth factor 2,[31] which is associated with metabolic diseases in later life.[32] Since the use of donor oocytes is associated with preeclampsia, it is reasonable to consider whether there is a concomitant increased risk for poor neonatal outcomes that is elevated above those found in ART offspring conceived with autologous oocytes.

Accordingly, there is a need to review and summarize the literature related to conceptions after oocyte donation to provide a knowledge base to inform reproductive technology

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practitioners and patients. The aims of this review were to summarize the published literature on neonatal outcomes such as birth weight, gestational age, and BD, for conceptions after oocyte donation in comparison to those conceived from autologous oocytes and spontaneous conceptions.

Methods

Literature search

A computerized literature search was conducted on articles published up to November 2012 in the online databases PubMed, EMBASE and Cochrane Reviews to identify studies containing data on neonatal health outcomes from donor oocytes.

The literature search comprised a three-stage process. First, relevant articles known to the authors were used to identify keywords along with a search of the U.S. National Library of Medicine MeSH (medical subject headings) database to identify appropriate search headings. Second, MeSH terms and other identified keywords were used to search the online databases. Search results were then analysed to determine specificity and to refine search terms, and filtered based on human not animal studies. Finally, the references of articles fitting the criteria were examined and online searches were implemented to find related articles.

Two main search categories were created and were termed 'Techniques', these were: oocyte donation and reproductive techniques. The term 'reproductive techniques' was chosen as a catch-all phrase. Two descriptors of human and donor were chosen to filter out animal studies and autologous treatments (own gametes). Three further qualifiers were implemented to each of the two techniques plus descriptor searches to refine the results. These qualifiers were: outcome*, morbidity, and adverse effects. The * wildcard was implemented to cover studies whose keywords implemented outcomes *v.* outcome. Search terms are also presented in Supplementary Table 1 for reference.

Eligibility and selection

Article selection and eligibility was performed by D.H.A. and verified by S.de L. according to the following PICOS criteria: *Participants*; cohorts of neonates that had neonatal health data presented in a study. *Interventions*; the treatment group must be comprised of a cohort of neonates conceived through fertility treatment of their parents with donated oocytes. The treatment group data must be appropriately segregated from comparison group data and not subsumed into larger combined data sets. *Comparators*; comparison cohorts could include offspring conceived through fertility treatment with autologous oocytes or general population data of spontaneous conceptions. *Outcomes*; studies to be included must report neonatal health outcomes such as (but not restricted to), birth weights, PD and BD (as determined by the publishing authors). Studies that only focused on live-birth rates or were case studies of single

or few outcomes were excluded. *Study design;* only those observational case-controlled studies that used a treatment-cohort and comparison-cohort, or those studies involving a treatment-cohort that was compared to published, or public health data for that specific region and within 10 years of the study were included in the review. This was to remove any natural variation occurring between populations and between given time points. Published articles were restricted to the English language to allow for careful analysis of the study to ensure accurate data extraction as terminology and reporting methods varied considerably. There was no time restriction posed on publication dates, however, EMBASE would only allow a search from 1980. Database search results were downloaded into Endnote then analysed by their titles and abstracts. Some articles were initially included as they could not be excluded based on their titles or abstracts, and were subsequently excluded following a full review of the text article (Fig. 1). Any disagreement was resolved via discussion.

Data extraction

The following data were recorded by D.H.A. from the eligible studies: citation data, country, comparison type (autologous cohort, published data), number of offspring in treatment/comparison group, if cryopreservation of oocytes was used, and specific neonatal health outcomes. Data were recorded onto a specially designed data extraction form. Specific health outcomes included birth weights, chromosomal or congenital malformations (BD), PD/gestational age, IUGR, and singletons *v.* multiple births (Table 1). Maternal age and parity were also extracted to assess confounding where applicable. Multiple birth is a known predictor of increased adverse outcomes[33,34] and was therefore a confounder to the analysis unless the data were stratified and extracted where presented. Oocyte cryopreservation is also a potential confounder as its effects on neonatal outcomes are poorly characterized, and therefore data were extracted where possible.

Data referring to previously published data or general population databases, but that did not record the actual outcome data, were not included in meta-analysis. No authors were contacted for missing or obscure data.

Meta-analysis

Meta-analyses of dichotomous outcomes data of low birth weight (LBW), very low birth weight (VLBW), PD and BD were performed according to Mantel-Haenszel methods, using a fixed effects model, risk ratios, 95% confidence intervals, and assessment of statistical heterogeneity using Cochrane's Q test and I^2 statistic. Continuous mean birth weight and gestational age data were analysed by inverse variance with fixed effects and 95% confidence intervals to determine the mean difference. Heterogeneity of data were determined by the I^2 value and is considered significant when $I^2 > 65\%$. Sensitivity analysis of studies that presented overlapping data were performed by conducting separate meta-analysis with those studies removed
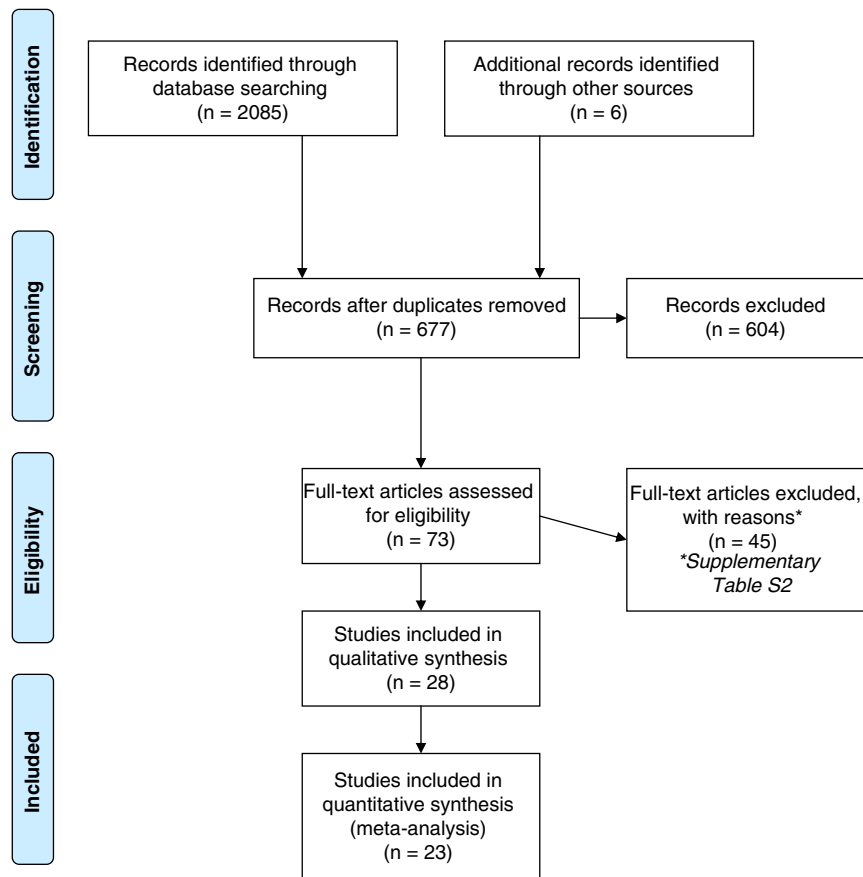
Fig. 1. PRISMA flowchart for identifying studies for inclusion in the review.

to determine any influence on data. All analyses were performed using Review Manager (RevMan) Version 5.2.8 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2012). Publication bias was assessed by visual analysis of funnel plots constructed in RevMan for asymmetry.

Risk of bias in individual studies

Included studies were assessed for methodological quality and the risk of bias using a modification of the Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument (JBI-MAStARI), with critical appraisal criteria for comparable cohort/case control studies.[35] Studies were assessed on the following criteria; Are patients in cohorts representative of patients typically receiving fertility treatment (for example, do they only include patients who may have been treated for ovarian cancer)? Are the patients at a similar point in the course of their condition/illness (do they describe how many times the patient had received treatment)? Has bias been minimized in relation to selection of cases and of comparators? Were singleton *v.* multiple births identified and strategies to deal with them stated? (If singleton *v.* multiples was described but all of the outcome data relevant to the review was not stratified then = No); Are other confounding factors identified and strategies to deal with them stated? Was cryopreservation of oocytes or the use of fresh oocytes adequately described, and were they appropriately stratified if both were included? Are outcomes assessed using objective criteria? Were outcomes measured in a reliable way? Was appropriate statistical analysis used?

Results

Searching of the three databases yielded 2085 articles with another six identified by hand-searching references lists. Duplicate removal reduced potential articles to 677. After screening the article titles and abstracts, 73 full-text publications were reviewed leaving a total of 28 studies to be included in the review and, of these, 23 were included in a meta-analysis (Fig. 1).

A summary of the characteristics and outcomes of all studies included in this review is presented in Table 1. Studies removed and the reasons for exclusion are presented in Supplementary Table S1.

There was a large amount of heterogeneity in the presentation of published outcomes. Subsequently, meta-analysis was only performed for outcomes that presented comparable statistical outcomes. The five studies not included in meta-analysis did not present comparable outcome data and have been summarized in the text.

Table 1. *Donor oocyte offspring health outcomes*

Study	Donation treatment(s) and sample size	Comparison and sample size	Frozen or fresh	Specific results
Gibbons et al.[36] United States	Oocyte 10,176	Autologous oocyte 49,252	Fresh	BW 3236 ± 652.7 v. 3240.1 ± 607.4 g LBW OR 1.21 v. 1 VLBW OR 1.28 v. 1 Gestational age 37.4 ± 2.4 v. 37.7 ± 2.2
Zegers-Hochschild et al.[37] South and Central America	Oocyte 73	Autologous oocyte 90	Not Specified	Singleton BW 2980 ± 446 v. 3170 ± 517 g Tw BW 2390 ± 577 v. 2057 ± 572 g ($P < 0.05$) Mult BW 1658 ± 452 v. 1365 ± 465 g ($P = 0.05$) Singleton GA 37.6 v. 38.5 (not significant) Tw GA 36.3 v. 34.7 (not significant)
Krieg et al.[38] United States	Oocyte 71 (pregnancies)	Autologous oocyte 108 (pregnancies)	Not Specified	BW 2835.6 ± 693.52 v. 3081.6 ± 674.29 g ($P = 0.02$) GA 37.0 (3.00 S.D.) v. 38.1 (2.61 S.D.) weeks ($P = 0.01$) Not significant when adjusted for multiple gestations IUGR OR 1.35 (0.67–2.72)
Söderström-Anttila et al.[39] Finland and Sweden	Oocyte 61 (67.2% S, 32.8% Mult)	Autologous oocyte 126 (54% S, 46% Mult)	Both	BW singletons 3338 ± 740 v. 3475 ± 630 g LBW singletons 10 v. 7% PD singletons 13 v. 7% SGA singletons 5 v. 6% Singletons in hospital (>7days) 36 v. 13 ($P < 0.01$) BW multiples 2216 ± 689 v. 2582 ± 556 g ($P < 0.05$) LBW multiples 50 v. 39% PD multiples 30 v. 48% SGA multiples 40 v. 24% Multiples admitted to ICU 60 v. 24 ($P < 0.01$)
Porreco et al.[40] United States	Embryo/oocyte 35 (pregnancies)	Autologous oocyte 32 (pregnancies)	Not Specified	BW 2446 ± 784 v. 2442 ± 687 g GA all births 36.9 ± 2.8 v. 37.2 ± 2.6 GA multiples 35.4 ± 2.6 v. 35.8 ± 3.2 PD 39 v. 29%
Friedman et al.[41] United States	Oocyte 22	Autologous oocyte 22	Unclear	BW 2924 ± 703 v. 2374 ± 822 g ($P < 0.005$) GA 35 (29–41) v. 38 (35–42) ($P < 0.01$)
Nelson and Lawlor[60] United Kingdom	Oocyte Total 144,018 donor plus own	Autologous oocyte Included in N of 144,018	Fresh	LBW donor 1 v. own 0.42 (0.26–0.68) ($P < 0.001$) PD donor 1 v. own 0.41 (0.26–0.64) ($P < 0.001$)
Kalra et al.[42] United States	Oocyte Fresh 5595 Frozen 3072	Autologous oocyte Fresh 20,916 Frozen 10,906	Both	LBW fresh 11.5 v. 10% LBW frozen 11.3 v. 7.2% PD fresh 19.3 v. 16% PD frozen 20.7 v. 15.8% PD LBW fresh 32.7 v. 34.1% PD LBW frozen 33.1 v. 23.8% Term LBW fresh 2.2 v. 2.5% Term LBW frozen 1.7 v. 1.2%
Sunderam et al.[43] United States	Oocyte 2995	Autologous oocyte 18,603	Fresh	LBW 12 v. 9.3% ($P < 0.01$) VLBW 2.6 v. 1.9% ($P < 0.01$) PD 17 v. 13.4% ($P < 0.01$) PD LBW 9.3 v. 6.7% ($P < 0.01$) PD VLBW 2.5 v. 1.9% ($P < 0.01$) Term LBW 2.7 v. 2.7% ($P < 0.01$) Term VLBW (0.1 v. 0%)

Wright et al.[44] United States	Oocyte 2864	Autologous oocyte 17,642	Fresh	LBW 11 v. 9.5% (P<0.01) VLBW 2 v. 1.7% PD 16.9 v. 13.4% (P<0.01) PD LBW 9 v. 6.9% Term LBW 2.1 v. 2.7% (P<0.01)
Thapar et al.[61] United Kingdom	Oocyte 146	Autologous oocyte 378	Not Specified	LBW singletons 13.6 v. 6.7% LBW all deliveries 23.4 v. 14.7%
Wright et al. [45] United States	Oocyte 2772	Autologous oocyte 17,230	Fresh	LBW 10.4 v. 9.5% (P<0.01) VLBW 1.9 v. 1.8% PD 16.2 v. 13.4% (P<0.01) PD LBW 8.3 v. 6.9% Term LBW 2.1 v. 2.5% (P<0.01)
Wright et al.[46] United States	Oocyte 2507	Autologous oocyte 16,082	Fresh	LBW 11.2 v. 9.3% (P<0.01) VLBW 2.3 v. 1.9% PD 17.6 v. 13.4% (P<0.01) PD LBW 9.1 v. 6.9% (P<0.01) Term LBW 2.1 v. 2.4% (P<0.01)
Wright et al.[47] United States	Oocyte 2199	Autologous oocyte 14,615	Fresh	LBW 10.7 v. 9.3% (P<0.01) VLBW 2.1 v. 1.9% PD 16.3 v. 13.3% (P<0.01) PD LBW 9 v. 7% (P<0.01) Term LBW 1.8 v. 2.3% (P<0.01)
Schieve et al.[48] United States	Oocyte 6432 (total) 899 (1996) 1019 (1997) 1250 (1998) 1459 (1999) 1805 (2000)	Autologous oocyte 47,586 (total) 6943 (1996) 8119 (1997) 9578 (1998) 10,511 (1999) 12,435 (2000)	Fresh	LBW 15.2 v. 13.7% (1996), 13 v. 13.5% (1997), 13.1 v. 12% (1998) 10 v. 9.9% (1999), 10.6 v. 9.1% (2000) VLBW 3.1 v. 2.2% (1996), 3.8 v. 3.1% (1997), 2 v. 2.1% (1998) 1.9 v. 1.8% (1999), 2.3 v. 1.9% (2000) PD 18.5 v. 13% (1996), 17.3 v. 12.7% (1997), 18.2 v. 13.1% (1998) 15.2 v. 12.2% (1999), 16.2 v. 13.1% (2000) PD LBW 8.8 v. 6.7% (1996), 8.1 v. 6.5% (1997), 8.9 v. 6.7% (1998) 7.5 v. 6.2% (1999), 8.2 v. 6.4% (2000) Term LBW 6.3 v. 6.9% (1996), 5 v. 6.7% (1997), 4.1 v. 5.2% (1998) 2.6 v. 3.7% (1999), 2.4 v. 2.5% (2000)
Sheffer-Mimouni et al.[62] Israel	Oocyte 134	General population Published data	Not Specified	PD 14.9 v. 7% ConMal 2.2% v. gen pop (no difference)
Corradetti et al.[63] Italy	Oocyte 14	Autologous oocyte 28	Unclear	IUGR 21.4 v. 7.1% (P<0.011)
Pados et al.[64] Europe, Lebanon and South America	Oocyte 60	Autologous oocyte and General population Published data	Both	IUGR 11.5% (donor) v. 17% (own) v. 3–7% (gen pop)
SART and ASRM[49] United States	Oocyte 2458 (56.5% S, 37.5% Tw, 6% Mult)	Autologous oocyte 17,677 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	BD 1.9 v. 1.6%
SART and ASRM[50] United States	Oocyte 1849 (59.7% S, 35.6% Tw, 4.7% Mult)	Autologous oocyte 14,314 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	BD 1.3 v. 1.8%
SART and ASRM[51] United States	Oocyte 1743 (58.9% S, 35.8% Tw, 5.3% Mult)	Autologous oocyte 11,342 (63.4% S, 29.6% Tw, 7% Mult)	Fresh	BD 0.6 v. 0.7%

Table 1. *Continued*

Study	Donation treatment(s) and sample size	Comparison and sample size	Frozen or fresh	Specific results
SART and ASRM[52] United States	Oocyte 1239 (61.8% S, 32.3% Tw, 5.9% Mult)	Autologous oocyte 6513 (63.7% S, 28.3% Tw, 6.5% Mult)	Fresh	BD 2.1 *v.* 2.7%
SART and ASRM[53] United States	Oocyte 1018 (59.6% S, 35% Tw, 5.4% Mult)	Autologous oocyte 7034 (65.9% S, 27.5% Tw, 5.8% Mult)	Fresh	BD 1.8 *v.* 2.3%
AFS and SART[54] United States	Oocyte 735 (62.9% S, 31.5% Tw, 4.1% Mult)	Autologous oocyte 5798 (67.3% S, 26% Tw, 6.2% Mult)	Fresh	BD 1.7 *v.* 1.9%
SART and AFS[55] United States	Oocyte 372 (66.8% S, 27.6% Tw, 5.6% Mult)	Autologous oocyte 3930 (70% S, 25% Tw, 4.8% Mult)	Fresh	BD 2.1 *v.* 1.5%
MRI *et al.*[58] United States	Oocyte 167 (45.8% S, 40.2% Tw, 14% Mult)	Autologous oocyte 3110 (52.8% S, 37.1% Tw, 10.1% Mult)	Fresh	ConMal 0.56 *v.* 1.22% ChAb 0 *v.* 0.7%
MRI *et al.*[57] United States	Oocyte 112 (47.3% S, 44.6% Tw, 8.1% Mult)	Autologous oocyte 2876 (50.8% S, 39.5% Tw, 9.7% Mult)	Fresh	ConMal 2.7 *v.* 0.9% ChAb 2.7 *v.* 1.2%
MRI *et al.*[56] United States	Oocyte 50 (46% S, 48% Tw, 6% Mult)	Autologous oocyte 2133 (56.9% S, 33.4% Tw, 9.7% Mult)	Fresh	ConMal 0 *v.* 0.84% ChAb 0 *v.* 0.75%

BW, birth weight; LBW, low birth weight <2500 g; VLBW, very low birth weight <1500 g; ConMal, congenital malformation; ChAb, chromosomal abnormalities; BD, birth defects; IUGR, intra-uterine growth retardation; PD, preterm delivery (<37 weeks); GA, gestational age (weeks); SGA, small for gestational age; S, singleton; Tw, twin; Mult, multiple (triplets or greater); OR, odds ratio; gen pop, general population.

Health outcomes for neonates conceived via donated oocytes. Sample sizes represented by statements such as 'published data' refers to the study citing data published elsewhere. Data are presented as donor *v.* control, *P* value for significance is only provided where *P* < 0.05. Comparison groups are autologous cohorts unless otherwise noted. General population refers to data obtained from spontaneous conceptions that have either been presented in 'published data' by other authors, or were part of a comparison cohort with specific data presented in the study.

Oocyte donation outcomes

A total of 28 studies investigating the health outcomes of people conceived via donated oocytes met the criteria for inclusion, 23 of which were included in the meta-analysis.[36–59] The remaining five studies were used in a qualitative analysis.[60–64] Two studies reported on comparisons to spontaneous conceptions but the data did not allow for meta-analysis. Subsequently all meta-analysis were comparisons against neonates conceived with autologous oocytes. From these studies a total of 201,628 neonatal health outcomes from donor oocytes and 432,361 from autologous oocytes have been analysed.

The actual number of offspring is overestimated due to the overlap of some studies[36,43–45] in relation to the data they obtained from the Society for Assisted Reproductive Technology databases covering the same years. We did not have access to the raw data and therefore the exact number cannot be ascertained, however, a sensitivity analysis was conducted to determine if it affected the meta-analysis outcomes (described later). The majority of the studies represented national data obtained from multicentres (71.4%), of which most were from the United States of America [data from Society for Assisted Reproductive Technology (SART) and Centers for Disease Control and Prevention (CDC)], while the single largest study was from a national study in the United Kingdom with data collected by the HFEA (Human Fertilisation and Embryology Authority). There is no consensus in the types of outcomes data these studies collected.

Cryopreservation data were recorded in some studies, however, the data were either poorly stratified, or in some instances was cryopreserved embryos created from donated oocytes and therefore could not be used in a meta-analysis. Consequently we do not report on the effects of cryopreservation on donated oocyte outcomes, however, we have left references to which studies noted cryopreservation in Table 1. Subsequently data will include both fresh and cryopreserved outcomes unless otherwise specified.

Oocyte donation birth weights

One of the most common outcomes reported was birth weights, which also included the categories of LBW < 2500 g, VLBW < 1500 g and IUGR or small for gestation age.

Ten studies reported a significant reduction in either the birth weights ($P = 0.02$),[38] or increased incidences of low birth weight category births (($P < 0.001$),[60] ($P < 0.01$[43–47]), IUGR ($P < 0.011$),[63] or increased odds ratios for low (1.21 *v.* 1)[36] or very low birth weights (1.28 *v.* 1)[36] of children conceived from donated oocytes when compared to those conceived from autologous oocytes. A further study found a similar significance but only in multiples and not singletons ($P < 0.05$).[39] Another two studies reported a higher incidence of LBW for donor oocyte neonates, but did not conduct statistical analysis on the outcome.[42,61] The four studies reporting no significant difference in birth weights or higher birth weights in donor oocyte neonates

were associated with the smallest sample sizes,[37,39–41] while studies reporting significant differences were associated with large multicentre national cohorts.[36,42–47,60]
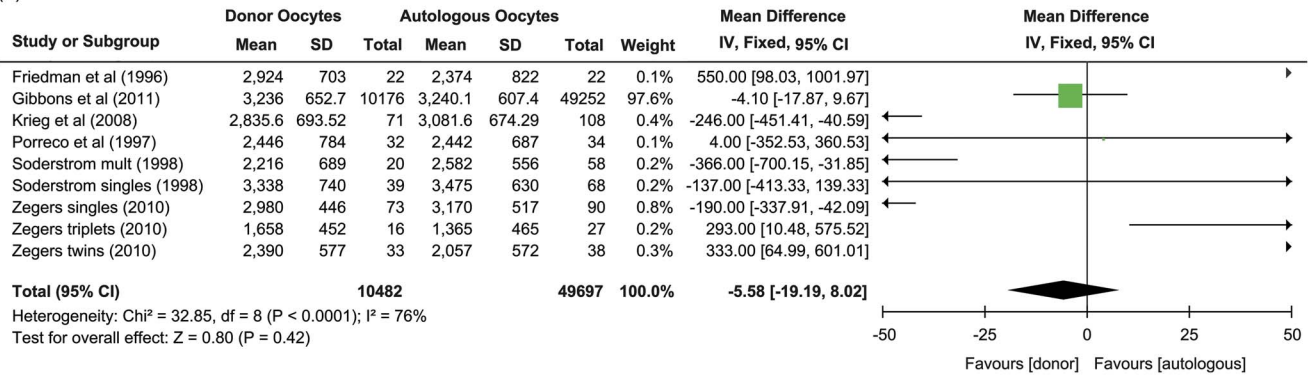
Meta-analysis of mean birth weights showed that donor oocyte neonates (singleton and multiple deliveries) had a lower mean difference but was not statistically different to control cohorts (autologous oocytes) (mean difference −5.58 g, CI: −19.19 to −8.02 g, $P = 0.42$, $I^2 = 76\%$) (Fig. 2a). When multiple deliveries were excluded, the outcome was relatively unchanged (mean difference −4.91 g, CI: −18.63 to −8.81 g, $P = 0.48$, $I^2 = 26\%$), even though heterogeneity was improved. These data are extensively influenced by the publication of Gibbons *et al.* who used a 3-year data set from U.S. national data obtained by the SART.[36] Donor oocyte neonates were at an increased risk ratio (RR: 1.18, CI: 1.14–1.22, $P < 0.00001$, $I^2 = 36\%$) observed for being born <2500 g (LBW) when compared to autologous oocytes (Fig. 2b). Schieve *et al.* stratified the data into years and subsequently each year was treated as a separate study to match the data from other studies that also reported on annual CDC and SART data (the Gibbons *et al.* data from the continuous data analysis of mean birth weights could not be similarly stratified as it was pooled data). Similarly to LBW, the risk of being born below 1500 g (VLBW) was increased for those conceived from donor oocytes compared to autologous oocytes (RR: 1.24, CI: 1.15–1.35, $P < 0.00001$, $I^2 = 32\%$) (Fig. 2c). VLBW was the only outcome measure that was of fresh donor oocytes only. These birth weight outcomes were for all neonates irrespective of whether they were born preterm (<37 weeks), at term (37–42 weeks), or post term (>42 weeks).

The data reported by Gibbons *et al.*[36] and Kalra *et al.*[42] covered SART data from 2004 to 2006, which overlapped with the SART data (same years) reported by Wright *et al.*[44,45] and Sunderam *et al.*,[43] however, outcome measures and numbers differed. Subsequently, they were included in the review and meta-analysis. To determine if the inclusion of Gibbons *et al.* and Kalra *et al.* adversely affected the meta-analysis, a sensitivity analysis was performed whereby they were removed from the meta-analysis. The outcomes for donor oocyte neonates was similar irrespective of the exclusion or inclusion of Gibbons *et al.* and Kalra *et al.* with LBW (excluded RR: 1.14, CI: 1.09–1.19, $P < 0.00001$, $I^2 = 31\%$), (included RR: 1.18, CI: 1.14–1.22, $P < 0.00001$, $I^2 = 36\%$), and VLBW (excluded RR: 1.23, CI: 1.12–1.36, $P < 0.0001$, $I^2 = 39\%$), (included RR: 1.24, CI: 1.15–1.35, $P < 0.00001$, $I^2 = 32\%$).

Oocyte donation PD

A total of 10 studies reported on the incidences of being born prematurely (PD < 37 weeks).[40,42–48,60,62] Of these ten studies, six reported that neonates conceived of donor oocytes were significantly more likely to be born PD ($P < 0.001$),[60] ($P < 0.01$).[43–47] Kalra *et al.* and Schieve *et al.* did not statistically analyse the donor *v.* autologous oocyte results.[42,48] Porreco *et al.* reported a higher percentage of donor oocyte neonates

(a)

Study or Subgroup	Donor Oocytes			Autologous Oocytes			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Friedman et al (1996)	2,924	703	22	2,374	822	22	0.1%	550.00 [98.03, 1001.97]
Gibbons et al (2011)	3,236	652.7	10176	3,240.1	607.4	49252	97.6%	-4.10 [-17.87, 9.67]
Krieg et al (2008)	2,835.6	693.52	71	3,081.6	674.29	108	0.4%	-246.00 [-451.41, -40.59]
Porreco et al (1997)	2,446	784	32	2,442	687	34	0.1%	4.00 [-352.53, 360.53]
Soderstrom mult (1998)	2,216	689	20	2,582	556	58	0.2%	-366.00 [-700.15, -31.85]
Soderstrom singles (1998)	3,338	740	39	3,475	630	68	0.2%	-137.00 [-413.33, 139.33]
Zegers singles (2010)	2,980	446	73	3,170	517	90	0.8%	-190.00 [-337.91, -42.09]
Zegers triplets (2010)	1,658	452	16	1,365	465	27	0.2%	293.00 [10.48, 575.52]
Zegers twins (2010)	2,390	577	33	2,057	572	38	0.3%	333.00 [64.99, 601.01]
Total (95% CI)			**10482**			**49697**	**100.0%**	**-5.58 [-19.19, 8.02]**
Heterogeneity: Chi² = 32.85, df = 8 (P < 0.0001); I² = 76%								
Test for overall effect: Z = 0.80 (P = 0.42)								

(b)

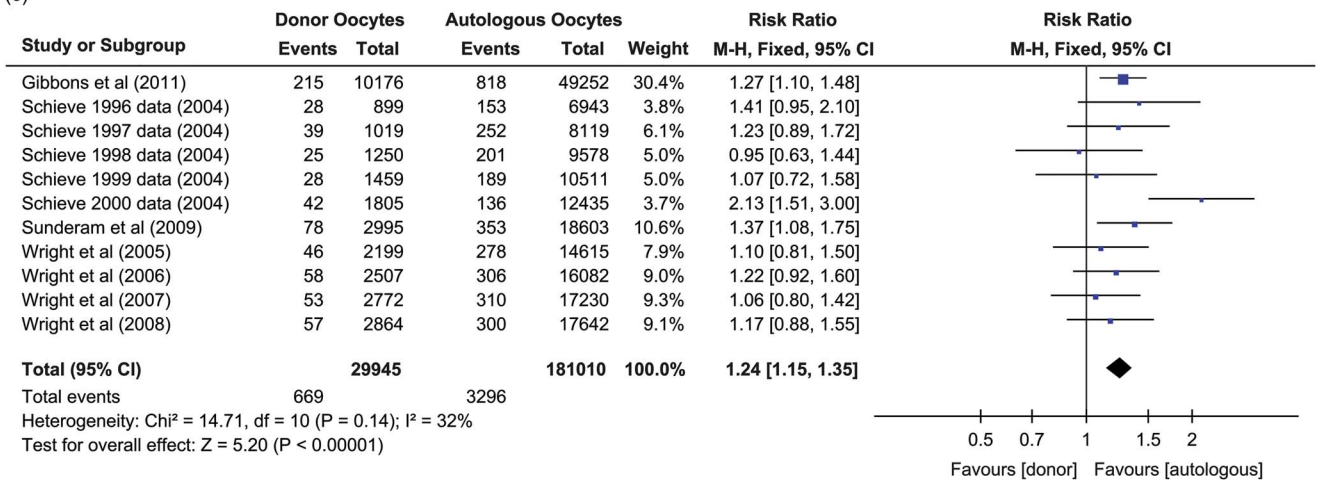| Study or Subgroup	Donor Oocytes		Autologous Oocytes		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Gibbons et al (2011)	1140	10176	4647	49252	25.3%	1.19 [1.12, 1.26]
Kalra et al (2011)	990	8667	2876	31822	19.6%	1.26 [1.18, 1.35]
Schieve 1996 data (2004)	137	899	951	6943	3.5%	1.11 [0.94, 1.31]
Schieve 1997 data (2004)	132	1019	1096	8119	3.9%	0.96 [0.81, 1.14]
Schieve 1998 data (2004)	164	1250	1149	9578	4.2%	1.09 [0.94, 1.27]
Schieve 1999 data (2004)	146	1459	1040	10511	4.0%	1.01 [0.86, 1.19]
Schieve 2000 data (2004)	191	1805	1132	12435	4.6%	1.16 [1.01, 1.34]
Soderstrom mult (1998)	10	20	23	58	0.2%	1.26 [0.73, 2.17]
Soderstrom singles (1998)	4	39	5	68	0.1%	1.39 [0.40, 4.89]
Sunderam et al (2009)	359	2995	1730	18603	7.6%	1.29 [1.16, 1.43]
Thapar et al 2007	34	146	55	378	0.5%	1.60 [1.09, 2.35]
Wright et al (2005)	235	2199	1359	14615	5.6%	1.15 [1.01, 1.31]
Wright et al (2006)	281	2507	1495	16082	6.4%	1.21 [1.07, 1.36]
Wright et al (2007)	288	2772	1637	17230	7.2%	1.09 [0.97, 1.23]
Wright et al (2008)	315	2864	1676	17642	7.4%	1.16 [1.03, 1.30]
Total (95% CI)		**38817**		**213336**	**100.0%**	**1.18 [1.14, 1.22]**
Total events	4426		20871			
Heterogeneity: Chi² = 21.75, df = 14 (P = 0.08); I² = 36%						
Test for overall effect: Z = 10.48 (P < 0.00001)						

(c)

| Study or Subgroup	Donor Oocytes		Autologous Oocytes		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Gibbons et al (2011)	215	10176	818	49252	30.4%	1.27 [1.10, 1.48]
Schieve 1996 data (2004)	28	899	153	6943	3.8%	1.41 [0.95, 2.10]
Schieve 1997 data (2004)	39	1019	252	8119	6.1%	1.23 [0.89, 1.72]
Schieve 1998 data (2004)	25	1250	201	9578	5.0%	0.95 [0.63, 1.44]
Schieve 1999 data (2004)	28	1459	189	10511	5.0%	1.07 [0.72, 1.58]
Schieve 2000 data (2004)	42	1805	136	12435	3.7%	2.13 [1.51, 3.00]
Sunderam et al (2009)	78	2995	353	18603	10.6%	1.37 [1.08, 1.75]
Wright et al (2005)	46	2199	278	14615	7.9%	1.10 [0.81, 1.50]
Wright et al (2006)	58	2507	306	16082	9.0%	1.22 [0.92, 1.60]
Wright et al (2007)	53	2772	310	17230	9.3%	1.06 [0.80, 1.42]
Wright et al (2008)	57	2864	300	17642	9.1%	1.17 [0.88, 1.55]
Total (95% CI)		**29945**		**181010**	**100.0%**	**1.24 [1.15, 1.35]**
Total events	669		3296			
Heterogeneity: Chi² = 14.71, df = 10 (P = 0.14); I² = 32%						
Test for overall effect: Z = 5.20 (P < 0.00001)						

Fig. 2. Forest plots of birth weight outcomes of neonates from donor oocytes *v.* autologous oocytes; (*a*) mean differences of birth weights, (*b*) risk ratio for being born of low birth weight < 2500 g, (*c*) risk ratio for being born of very low birth weight <1500 g.

born PD, but it was not statistically significant (*P* value not reported).[40] Meta-analysis showed a significant increased risk of being born PD as a result of using donor rather than autologous

oocytes (RR: 1.26, CI: 1.23–1.30, $P < 0.00001$, $I^2 = 0\%$) (Fig. 3a). Five studies investigated gestational age in absolute terms (age in weeks) with two finding that donor oocytes were
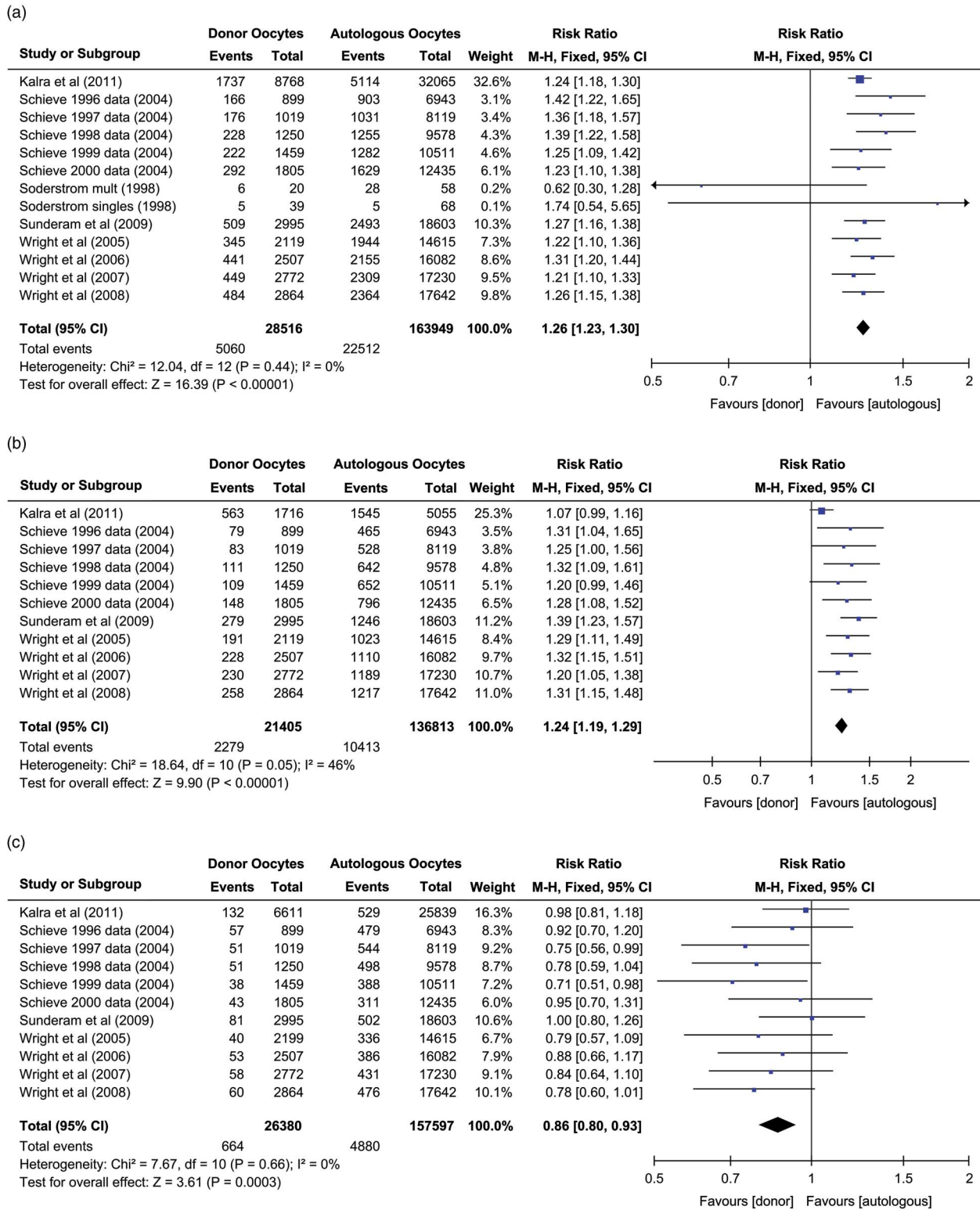
Fig. 3. Forest plots of preterm and term delivery outcomes of neonates from donor oocytes *v.* autologous oocytes; (*a*) risk ratio for being born preterm (<37 weeks), (*b*) risk ratio for being born preterm and of low birth weight, (*c*) risk ratio of being born term and low birth weight.

more likely to be born at a lower gestational age ($P < 0.01$),[38,41] while the other three ($P = 0.563$),[36] (P value not reported),[37,40] found no difference when compared with autologous oocyte

gestations. The Krieg *et al.* gestational age data were also associated with a lower birth weight. By contrast, Zegers-Hochschild *et al.* found no significant difference in singleton or twin

gestational ages (*P* value not reported).[37] Additionally, Porreco *et al.* found no difference between groups in respect to birth weights, gestational age (including singleton *v.* multiple delivery analysis) and PD.[40] Meta-analysis of the continuous data on gestational age showed that donor oocytes were born significantly earlier by 0.3 weeks when compared to autologous oocytes (mean difference −0.3 weeks, CI: −0.35 to −0.25 weeks, $P < 0.00001$, $I^2 = 40\%$) (Zegers-Hochschild *et al.*[37] was excluded due to lack of standard deviation data).

Oocyte donation birth weight with PD

Seven studies correlated the birth weight results with the incidences of the neonates being born prematurely.[42–48] Of these, three found a significant correlation in donor oocyte neonates when compared with autologous oocyte neonates being born PD and LBW ($P < 0.01$).[43,46,47] One study also showed an association of PD with being born VLBW ($P < 0.01$).[43] Schieve *et al.* did not perform statistical analysis of donor *v.* autologous oocytes; however, in every year of data there was a higher percentage of donor oocyte neonates born PD with LBW (8.8 *v.* 6.7% (1996), 8.1 *v.* 6.5% (1997), 8.9 *v.* 6.7% (1998), 7.5 *v.* 6.2% (1999), 8.2 *v.* 6.4% (2000)).[48] The other two studies found no significant difference. Meta-analysis of the incidence of PD with LBW in donor oocytes showed a significant increased risk compared with autologous oocytes (RR: 1.24, CI: 1.19–1.29, $P < 0.00001$, $I^2 = 46\%$) (Fig. 3b).

Seven studies correlated the birth weight results with the incidences of the neonates being born at term.[42–48] For those born at term with donated oocytes there was a decreased risk of LBW (RR: 0.86, CI: 0.8–0.93, $P = 0.0003$, $I^2 = 0\%$) (Fig. 3c).

Oocyte donation BD

The reporting of BD was absent from recent analysis of donor oocyte outcomes but were presented in earlier studies by Medical Research International (MRI) *et al.*[56–58] Additionally, data collected by the SART from clinics in the United States from 1990 to 1997 reported on congenital malformations and BD,[49–53] and Sheffer-Mimouni *et al.*[62] reported on congenital malformations.[62] The MRI and SART data did not include statistical analysis but rather reported percentages of incidences in which a higher percentage of BD was observed in 3 of the 10 years (see Table 1). Sheffer-Mimouni *et al.* found no significant difference to the general population in Israel (statistics not reported).[62] Meta-analysis of BD showed no increased risk ratio for fresh donor *v.* fresh autologous oocytes, although a non-significant tendency to a lower risk was observed (RR: 0.89, CI: 0.75–1.05, $P = 0.15$, $I^2 = 48\%$) (Fig. 4). The data set from the BD meta-analysis contained the incidences of twin and multiple (triplets or higher order) birth occurrences. Donor oocyte neonates were more likely to be born as a twin or from higher order deliveries (RR: 1.1, CI: 1.07–1.13, $P < 0.00001$, $I^2 = 31\%$), in the cohorts included in the BD meta-analysis.

Oocyte donation other outcomes

Söderström-Anttila *et al.* also investigated the length of time neonates stayed in hospital before going home and the incidences of them being admitted to the intensive care unit (ICU).[39] The authors found a significant increase in the length of stay in the hospital of donor oocyte singleton neonates ($P < 0.01$), as well as an increase in the incidence of admissions to the ICU for donor oocyte multiple birth neonates ($P < 0.01$), when compared to autologous multiple birth oocytes.[39]

Effect of multiplicity on outcomes

Multiple births is a well known confounder for negative neonatal outcomes. Subsequently we assessed the risk ratios for the occurrences of multiple deliveries for the studies included in this review. As shown above, there was an increased risk
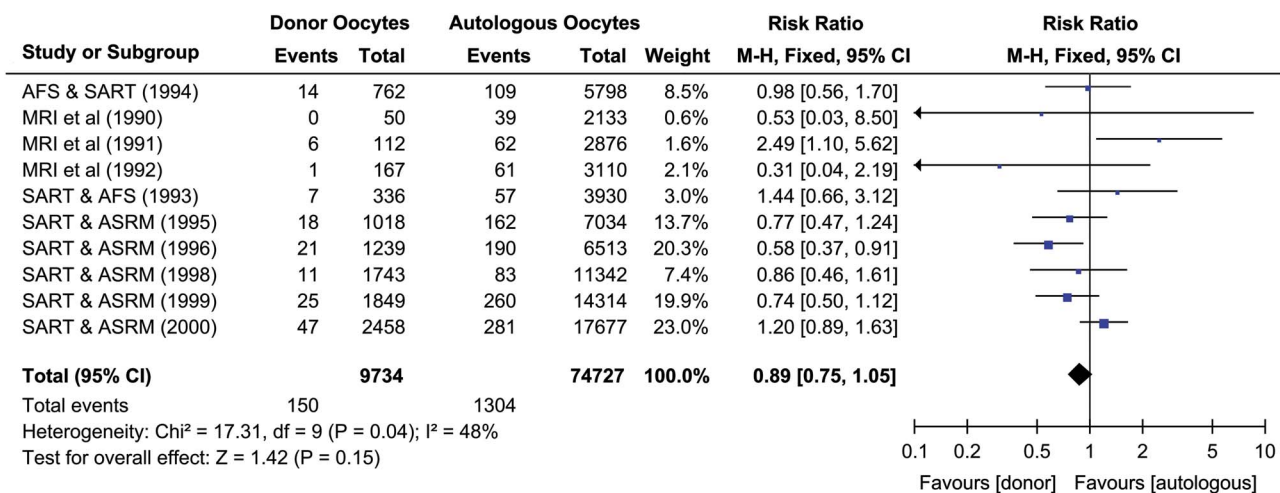
Study or Subgroup	Donor Oocytes Events	Donor Oocytes Total	Autologous Oocytes Events	Autologous Oocytes Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFS & SART (1994)	14	762	109	5798	8.5%	0.98 [0.56, 1.70]
MRI et al (1990)	0	50	39	2133	0.6%	0.53 [0.03, 8.50]
MRI et al (1991)	6	112	62	2876	1.6%	2.49 [1.10, 5.62]
MRI et al (1992)	1	167	61	3110	2.1%	0.31 [0.04, 2.19]
SART & AFS (1993)	7	336	57	3930	3.0%	1.44 [0.66, 3.12]
SART & ASRM (1995)	18	1018	162	7034	13.7%	0.77 [0.47, 1.24]
SART & ASRM (1996)	21	1239	190	6513	20.3%	0.58 [0.37, 0.91]
SART & ASRM (1998)	11	1743	83	11342	7.4%	0.86 [0.46, 1.61]
SART & ASRM (1999)	25	1849	260	14314	19.9%	0.74 [0.50, 1.12]
SART & ASRM (2000)	47	2458	281	17677	23.0%	1.20 [0.89, 1.63]
Total (95% CI)		**9734**		**74727**	**100.0%**	**0.89 [0.75, 1.05]**
Total events	150		1304			

Heterogeneity: Chi² = 17.31, df = 9 (P = 0.04); I² = 48%
Test for overall effect: Z = 1.42 (P = 0.15)

Fig. 4. Forest plots of birth defect risk ratios of neonates from donor oocytes *v.* autologous oocytes.

of multiple deliveries as a result of using donor rather than autologous oocytes (RR: 1.1, CI: 1.07–1.13, $P < 0.00001$, $I^2 = 31\%$), in the studies used for BD meta-analysis. The studies showing increased multiplicity were typically those published before 2000 and since that time there has been a greater awareness of the need to reduce the number of embryos implanted. For example the ASRM guidelines which described the maximum number of embryos to be implanted were introduced in 1998 but have been adjusted down over the course of the period since with resultant multiple pregnancies decreasing dramatically during that time.[59] Therefore it was important to determine whether the increased risk ratios observed in the outcomes reported above would still hold in an analysis of singleton outcomes.

Mean birth weights remained lower but still not significant for donor oocyte neonates when compared to autologous oocyte neonates (Singleton mean difference; −4.91 g, CI: −18.63 to –8.81 g, $P = 0.48$, $I^2 = 26\%$ v. All births mean difference −5.58 g, CI: −19.19 to –8.02 g, $P = 0.42$, $I^2 = 76\%$). The risk of being born of LBW as a result of using donor oocytes compared with autologous oocytes remained significant (Singleton RR: 1.17, CI: 1.12–1.23, $P < 0.00001$, $I^2 = 59\%$ v. All births RR: 1.18, CI: 1.14–1.22, $P < 0.00001$, $I^2 = 36\%$), as did being born of VLBW (Singleton RR: 1.31, CI: 1.11–1.54, $P = 0.001$, $I^2 = 65\%$ v. All births RR: 1.24, CI: 1.15–1.35, $P < 0.00001$, $I^2 = 32\%$), PD (Singleton RR: 1.27, CI: 1.22–1.32, $P < 0.00001$, $I^2 = 5\%$ v. All births RR: 1.26, CI: 1.23–1.30, $P < 0.00001$, $I^2 = 0\%$), as well as PD and LBW (Singleton RR: 1.17, CI: 1.10–1.24, $P < 0.00001$, $I^2 = 42\%$ v. All births RR: 1.24, CI: 1.19–1.29, $P < 0.00001$, $I^2 = 46\%$). Additionally the association of decreased risk of donor oocyte neonates being born at term of LBW also remained in the meta-analysis of singletons (Singleton RR: 0.86, CI: 0.77–0.96, $P = 0.007$, $I^2 = 2\%$ v. All births RR: 0.86, CI: 0.8–0.93, $P = 0.0003$, $I^2 = 0\%$). Controlling for multiple births in the meta-analysis of outcomes did not alter the increased risk of poor neonatal outcomes for donor oocyte neonate singletons when compared with autologous oocyte singletons.

Risk of bias

There was variation in the methodological quality of the studies included (Table 2). In general, the reporting of the length of time the woman had been receiving treatment (number of previous attempts) was poorly documented and even when such data were presented it was not stratified into donor v. autologous treatments. This lack of stratification also occurred frequently in the reporting of other confounders such as maternal age, parity, BMI, reasons for infertility and other demographic data. Singleton v. multiple deliveries was poorly stratified into donor v. autologous treatments in many of the studies.

Maternal age and parity data where reported are presented in Table 3. Mean birth weight meta-analysis incorporated 97.6% of weighted data adjusted and controlled for maternal ages and parity.[36] Of those studies reporting maternal ages

and low birth weight, the associations were conflicting. Gibbons *et al.* adjusted for maternal age and found no correlation with maternal age,[36] whereas the higher maternal ages of the donor oocyte cohort reported by Sunderam *et al.* were associated with increased risk of low birth weight and very low birth weight.[43] The single study reporting maternal age data in relation to PD, found donor oocyte cohort maternal ages to be proportionally higher compared to the autologous oocyte cohort and was associated with PD and PD with low birth weight.[43] Maternal age and parity data of included studies investigating BD were not reported.

Studies reporting outcomes such as birth weights, LBW, VLBW, GA and PD were deemed to be reporting objective criteria. However, those only reporting BD (or what was classified as congenital malformations) were more subjective in nature as BD can potentially be missed in the neonatal period. Five of the studies stated that the reporting of BD outcomes was poor and therefore the data set did not contain all BD data.[51–54] The study by Pados *et al.* did not have a comparison cohort but only referred to previously published work, which was limited,[64] while Corradetti *et al.* did not adequately describe the selection of comparators.[63]

Funnel plot analysis showed publication bias in oocyte donation health outcome meta-analysis for fresh oocyte BD, while birth weights were too heterogeneous. Outcome measures LBW, VLBW, PD, PD with LBW, and term with LBW were symmetrical. Funnel plot analysis of singleton outcomes showed that birth weight data again was too heterogeneous, and that LBW, PD, and term with LBW were symmetrical, while VLBW and PD with LBW were asymmetrical showing the presence of reporting bias.

Limitations of study

This review was limited by the restriction to three databases, limited hand-searching and the restriction to the English language. Methodological quality and reporting details in earlier publications was generally lower than later studies, which prevented the inclusion of some studies in meta-analysis.

From the data retrieved via this review, the lack of statistical analysis in some of these studies is a concern as is the ability for the studies to capture accurate data when self-reporting is involved. The AFS and SART[54], and SART and ASRM[51–53], reported that the incidence of BD were low but that 'more stringent requirements for follow-up and reporting' (P1126, P19, P703, P395, respectively) were to be implemented in subsequent years.[51–54] This suggests that the ability to accurately capture this data could be improved. Furthermore, in 2000 they suggested that there were still limitations on the data for birth outcomes,[49] thereby suggesting that the incidences of BD in all groups may be underreported.

The reporting of multiple deliveries was inconsistent and not all data were appropriately stratified for analysis of singleton v.

Table 2. *Critical appraisal and risk of bias of included studies*

Study	Representative patients	Similar point in condition	Minimized case selection bias	Singleton v. multiples	Other confounders	Cryopreservation	Objective criteria	Reliable outcomes	Appropriate statistics
						Criterion			
Gibbons et al.[36]	Yes	Unclear[a]	Yes	No[a]	Yes	Yes	Yes	Yes	Yes
Zegers-Hochschild et al.[37]	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Krieg et al.[38]	Yes	Unclear	Yes	No[a]	Yes	No	Yes	Yes	Yes
Söderström-Anttila et al.[39]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Porreco et al.[40]	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes
Friedman et al.[41]	Yes	Unclear	Yes	No	Yes	No	Yes	Yes	Yes
Nelson and Lawlor[60]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Kalra et al.[42]	Yes	Unclear[a]	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sunderam et al.[43]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright et al.[44]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Thapar et al.[61]	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	Yes
Wright et al.[45]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright et al.[46]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright et al.[47]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Schieve et al.[48]	Yes	Unclear	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sheffer-Mimouni et al.[62]	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	No[b]
Corradetti et al.[63]	Yes	Unclear	Unclear	No	No	No	Yes	Yes	Yes
Pados et al.[64]	Yes	Unclear	No[c]	No[a]	No[a]	No	Yes	Yes	No
SART and ASRM[49]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[50]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[51]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[52]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[53]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
AFS and SART[54]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and AFS[55]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
MRI et al.[58]	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No
MRI et al.[57]	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No
MRI et al.[56]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No

[a]Data presented but not stratified donor *v.* autologous, or not used in an analysis.
[b]Statistics used appropriately but did not analyse donor *v.* autologous.
[c]Comparison group was used but was published data not comparison cohort.

Table 3. *Maternal age and parity reporting of included studies*

Study	Maternal age details	Parity details
Gibbons *et al.*[36]	Data adjusted for maternal age	Data adjusted for parity
Zegers-Hochschild *et al.*[37]	(14% ⩽ 34 years, 25.1% 35–39 years, 60.9% ⩾ 40 years) *v.* (50% ⩽ 34 years, 34.6% 35–39 years, 15.4% ⩾ 40 years)	
Krieg *et al.*[38]	(42.7 ± 4.4 years) *v.* (41.3 ± 1.84 years)	(0.32 ± 0.528) *v.* (0.35 ± 0.569)
Söderström-Anttila *et al.*[39]	(33.5 ± 4.7 years) *v.* (33.4 ± 3.7 years)	84 *v.* 69% nulliparous
Porreco *et al.*[40]	(38.8 years (range 27–50)) *v.* (38.7 years (range 34–44))	89 *v.* 78% nulliparous
Sunderam *et al.*[43]	(12% < 35 years, 11.7% 35–37 years, 17.3% 38–40 years, 16.2% 40–42 years, 42.8% > 42 years) *v.* (56.3% < 35 years, 25.1% 35–37 years, 14.3% 38–40 years, 3.5% 40–42 years, 0.8% > 42 years)[a]	
Thapar *et al.*[61]	(37.88 ± 5.89 years) *v.* (34.14 ± 3.53 years)	
Corradetti *et al.*[63]	(range 32–50 years) *v.* (range 30–46 years)	

Only those studies reporting maternal age and parity are listed.
[a]A function of live birth delivery rates.

multiple birth outcomes. While rates of multiples were broken down in some studies, in some of these instances the outcome data were pooled rather than stratified and therefore meta-analysis could not be performed in a stratified manner for those studies, thereby reducing the number of studies available for meta-analysis of singleton data. However, when meta-analysis of the singleton data were performed, similar risk ratios for negative outcomes were observed suggesting that multiple birth confounding data did not significantly influence the analysis on outcomes.

Methodological quality and reporting of outcomes in a systematic way generally improved over time, with later studies better addressing the donor *v.* autologous outcomes question. Consistency in reporting, with increased analysis of confounders such as multiple deliveries, maternal age, parity and cryopreservation, can be improved.

Discussion

This review has demonstrated that donor oocyte neonates, when compared with autologous oocyte neonates, are at increased risk of being born of low birth weight, very low birth weight, preterm, preterm with low birth weight, and have a lower gestational age. The incidences of low birth weight were not increased, rather they were decreased when donor oocyte neonates were born at normal gestation. These correlations also occurred when controlling for multiple deliveries. However, singleton very low birth weight and PD with low birth weight analysis showed the presence of some reporting bias and more data is required to clarify these outcomes in singletons. The majority of comparison group data and all of meta-analysis comparison data were of autologous oocytes, of which only two studies of small sample size reported spontaneous conception

data as a comparison.[62,64] The use of autologous oocyte neonates as the comparison cohort rather than spontaneous conceptions is a more appropriate comparison as the manipulation of oocytes may influence neonatal outcomes and therefore strengthens the review findings.

Meta-analysis showed no increase in the incidences of BD occurring as a result of using donor *v.* autologous oocytes, but rather a non-significant decrease was observed. While several studies (particularly those involving SART data) reported on the incidences of multiple deliveries, the incidences of BD was not appropriately stratified by plurality to determine if the BD were occurring in the multiple deliveries, and subsequently could only be used to determine the risk ratio for all births as a result of using donated or autologous oocytes. The use of donor oocytes was correlated with multiple deliveries in the studies used for BD meta-analysis. While this is a known confounder, a lower risk of BD was observed. This would be consistent with oocytes being donated by women younger than the recipients and in whom lower incidences occur of poor quality oocytes such as those with aneuploidy.[65,66] In comparison to ART outcomes in general, the incidences of BD in donor oocyte neonates are less (ART birth defects RR: 1.32, CI: 1.24–1.42, $P = 0.000$, $I^2 = 47\%$).[3]

The results of this review suggest that the incidences of BD and or congenital malformations are not adversely affected by the use of fresh donor oocytes and that data should be collected on the BD incidences from neonates conceived with cryopreserved donor oocytes. This is pertinent considering that oocyte cryopreservation often involves the use of genotoxic cryoprotectants,[67] with some researchers reporting increased incidences of DNA damage.[68,69]

There was only one study investigating length of hospital stays and admissions to neonatal intensive care units (NICU)

for those neonates conceived with donor rather than autologous oocytes. The increased length of hospital stay and NICU admissions found by Söderström-Anttila et al. (including in singletons), has been corroborated since the review census date. Malchau et al. reported a significant increase in the percentage of donor oocyte singleton neonates entering NICU (24.2 v. 7.6%, P < 0.0001), and an increase in their length of stay (2.5 ± 7.5 v. 0.9 ± 5.8 days, P = 0.002).[70] Further investigation in this area is therefore warranted.

Additionally, others have reported increased negative neonatal outcomes following oocyte donation when compared to autologous oocytes of low birth weight, very low birth weight, PD, very PD, small for gestational age, and very small for gestational age;[2] and PD, and low birth weight[70] since the literature search was completed and support the findings of this review.

Patients undergoing treatment for infertility require accurate information, not only about the expected pregnancy and take home baby rates of the treatment, but also about the expected health of their infant and how this might be affected by the procedure. Clinicians involved in interventions for the treatment of infertility have an obligation to provide this information, to the best of their ability, in counselling couples about treatment choices.

Increased incidences of low birth weight, very low birth weight, lower gestational age, PD, PD with low birth weight, and preeclampsia that are correlated with the use of donor oocytes constitute obstetric risks that will pose a challenge for obstetricians in their provision of care. Preliminary evidence suggestive of increased NICU admissions associated with donor oocytes are also of concern. While low birth weight can be avoided in donor oocyte conceptions when the fetus reaches normal gestation, it is unclear if this is clinically possible or advisable, considering the correlation with preeclampsia. It could possibly be viewed that preeclampsia represents a far greater risk to mother and fetus than low birth weight and PD outcomes. Therefore preeclampsia would warrant the primary consideration of the obstetrician. Patients should be counselled on the gestational/perinatal risks so that they are fully informed of potential outcomes and therefore maintain full autonomy over their reproductive choices.

The results of this review also highlight other areas that require further investigation. Studies that specifically stratify and isolate negative neonatal outcomes as a direct consequence of preeclampsia rather than just as a correlation will help ascertain if the increased incidences are primarily the result of a significant immunological challenge or if a more minor immunological response can also produce these outcomes. Finally, studies are required that investigate the longitudinal outcomes into childhood and adulthood to determine if these negative neonatal outcomes resulting from their conception with donated oocytes also negatively impact their long term health as currently there are no such studies.

Due to poor neonatal outcomes of low birth weights and preterm deliveries being associated with increased incidences of morbidity and mortality in later life,[8–10] the donor oocyte cohort represent a significant health care burden for the individual and society. This is irrespective of any reasons as to why this cohort fares worse than autologous oocyte neonates or spontaneously conceived neonates.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S2040174415007898

References

1. Hart R, Norman RJ. The longer-term health outcomes for children born as a result of IVF treatment: Part I – General health outcomes. *Hum Reprod Update*. 2013; 19, 232–243.
2. Marino JL, Moore VM, Willson KJ, *et al*. Perinatal outcomes by mode of assisted conception and sub-fertility in an Australian data linkage cohort. *PLoS One*. 2014; 9, e80398.
3. Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. *Hum Reprod Update*. 2013; 19, 330–353.
4. Pinborg A, Wennerholm UB, Romundstad LB, *et al*. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update*. 2013; 19, 87–104.
5. Talaulikar VS, Arulkumaran S. Reproductive outcomes after assisted conception. *Obstet Gynecol Surv*. 2012; 67, 566–583.
6. McDonald SD, Han Z, Mulla S, *et al*. Preterm birth and low birth weight among *in vitro* fertilization singletons: a systematic review and meta-analyses. *Eur J Obstet Gynecol Reprod Biol*. 2009; 146, 138–148.
7. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ*. 2004; 328, 261.
8. Class QA, Rickert ME, Lichtenstein P, D'Onofrio BM. Birth weight, physical morbidity, and mortality: a population-based sibling-comparison study. *Am J Epidemiol*. 2014; 179, 550–558.
9. Calkins K, Devaskar SU. Fetal origins of adult disease. *Curr Probl Pediatr Adolesc Health Care*. 2011; 41, 158–176.
10. Barker DJP. *The Fetal and Infant Origins of Adult Disease*. 1992. BMJ Books: London.

11. Batcheller A, Cardozo E, Maguire M, DeCherney AH, Segars JH. Are there subtle genome-wide epigenetic alterations in normal offspring conceived by assisted reproductive technologies? *Fertil Steril*. 2011; 96, 1306–1311.

12. Tranquilli AL, Biondini V, Talebi Chahvar S, *et al*. Perinatal outcomes in oocyte donor pregnancies. *J Matern Fetal Neonatal Med*. 2013; 26, 1263–1267.

13. Klatsky PC, Delaney SS, Caughey AB, *et al*. The role of embryonic origin in preeclampsia: a comparison of autologous *in vitro* fertilization and ovum donor pregnancies. *Obstet Gynecol*. 2010; 116, 1387–1392.

14. Salha O, Sharma V, Dada T, *et al*. The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. *Hum Reprod*. 1999; 14, 2268–2273.

15. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. *Mol Aspects Med*. 2007; 28, 192–209.

16. Sargent IL, Borzychowski AM, Redman CW. Immunoregulation in normal pregnancy and pre-eclampsia: an overview. *Reprod Biomed Online*. 2006; 13, 680–686.

17. Ahn H, Park J, Gilman-Sachs A, Kwak-Kim J. Immunologic characteristics of preeclampsia, a comprehensive review. *Am J Reprod Immunol*. 2011; 65, 377–394.

18. Schiessl B. Inflammatory response in preeclampsia. *Mol Aspects Med*. 2007; 28, 210–219.

19. Backes CH, Markham K, Moorehead P, *et al*. Maternal preeclampsia and neonatal outcomes. *J Pregnancy*. 2011; 2011, 214365.

20. Challis JR, Lockwood CJ, Myatt L, *et al*. Inflammation and pregnancy. *Reprod Sci*. 2009; 16, 206–215.

21. Zetterström K, Lindeberg S, Haglund B, Magnuson A, Hanson U. Being born small for gestational age increases the risk of severe pre-eclampsia. *BJOG*. 2007; 114, 319–324.

22. Geelhoed JJ, Fraser A, Tilling K, *et al*. Preeclampsia and gestational hypertension are associated with childhood blood pressure independently of family adiposity measures: the Avon Longitudinal Study of Parents and Children. *Circulation*. 2010; 122, 1192–1199.

23. Jayet PY, Rimoldi SF, Stuber T, *et al*. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. *Circulation*. 2010; 122, 488–494.

24. Himmelmann A. Blood pressure and left ventricular mass in children and adolescents: the Hypertension in Pregnancy Offspring Study. *Blood Press Suppl*. 1994; 3, 1–46.

25. Davis EF, Newton L, Lewandowski AJ, *et al*. Pre-eclampsia and offspring cardiovascular health: mechanistic insights from experimental studies. *Clin Sci (Lond)*. 2012; 123, 53–72.

26. Davis EF, Lazdam M, Lewandowski AJ, *et al*. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics*. 2012; 129, e1552–e1561.

27. Wu CS, Sun Y, Vestergaard M, *et al*. Preeclampsia and risk for epilepsy in offspring. *Pediatrics*. 2008; 122, 1072–1078.

28. Wu CS, Nohr EA, Bech BH, *et al*. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol*. 2009; 201, 269.e1–269.e10.

29. Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. *Stroke*. 2009; 40, 1176–1180.

30. Mann JR, McDermott S, Bao H, Hardin J, Gregg A. Pre-eclampsia, birth weight, and autism spectrum disorders. *J Autism Dev Disord*. 2010; 40, 548–554.

31. Millis RM. Epigenetics and hypertension. *Curr Hypertens Rep*. 2011; 13, 21–28.

32. He J, Zhang A, Fang M, *et al*. Methylation levels at IGF2 and GNAS DMRs in infants born to preeclamptic pregnancies. *BMC Genomics*. 2013; 14, 472.

33. Skora D, Frankfurter D. Adverse perinatal events associated with ART. *Semin Reprod Med*. 2012; 30, 84–91.

34. Barrington KJ, Janvier A. The paediatric consequences of assisted reproductive technologies, with special emphasis on multiple pregnancies. *Acta Paediatr*. 2013; 102, 340–348.

35. Joanna Briggs Institute. *Reviewers' Manual: 2011 Edition*. 2011. Joanna Briggs Institute, University of Adelaide: Adelaide, Australia.

36. Gibbons WE, Cedars M, Ness RB, Society for Assisted Reproductive Technologies Writing Group. Toward understanding obstetrical outcome in advanced assisted reproduction: varying sperm, oocyte, and uterine source and diagnosis. *Fertil Steril*. 2011; 95, 1645–1649.

37. Zegers-Hochschild F, Masoli D, Schwarze JE, *et al*. Reproductive performance in oocyte donors and their recipients: comparative analysis from implantation to birth and lactation. *Fertil Steril*. 2010; 93, 2210–2215.

38. Krieg SA, Henne MB, Westphal LM. Obstetric outcomes in donor oocyte pregnancies compared with advanced maternal age in *in vitro* fertilization pregnancies. *Fertil Steril*. 2008; 90, 65–70.

39. Söderström-Anttila V, Tiitinen A, Foudila T, Hovatta O. Obstetric and perinatal outcome after oocyte donation: comparison with in-vitro fertilization pregnancies. *Hum Reprod*. 1998; 13, 483–490.

40. Porreco RP, Schoolcraft CL, Schoolcraft WB. Pregnancy outcome following donor embryo replacement. *J Matern Fetal Neonatal Med*. 1997; 6, 237–240.

41. Friedman F Jr, Copperman AB, Brodman ML, *et al*. Perinatal outcome after embryo transfer in ovum recipients. A comparison with standard *in vitro* fertilization. *J Reprod Med*. 1996; 41, 640–644.

42. Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through *in vitro* fertilization. *Obstet Gynecol*. 2011; 118, 863–871.

43. Sunderam S, Chang J, Flowers L, *et al*. Assisted reproductive technology surveillance – United States, 2006. *MMWR Surveill Summ*. 2009; 58, 1–25.

44. Wright VC, Chang J, Jeng G, Macaluso M, Centers for Disease Control and Prevention (CDC). Assisted reproductive technology surveillance – United States, 2005. *MMWR Surveill Summ*. 2008; 57, 1–23.

45. Wright VC, Chang J, Jeng G, Chen M, Macaluso M. Assisted reproductive technology surveillance – United States, 2004. *MMWR Surveill Summ*. 2007; 56, 1–22.

46. Wright VC, Chang J, Jeng G, Macaluso M. Assisted reproductive technology surveillance – United States, 2003. *MMWR Surveill Summ*. 2006; 55, 1–22.

47. Wright VC, Schieve LA, Reynolds MA, Jeng G. Assisted reproductive technology surveillance – United States, 2002. *MMWR Surveill Summ*. 2005; 54, 1–24.

48. Schieve LA, Ferre C, Peterson HB, *et al*. Perinatal outcome among singleton infants conceived through assisted reproductive

technology in the United States. *Obstet Gynecol.* 2004; 103, 1144–1153.

49. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1997 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 2000; 74, 641–653.

50. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 1996 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 1999; 71, 798–807.

51. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1995 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 1998; 69, 389–398.

52. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1994 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 1996; 66, 697–705.

53. Society for Assisted Reproductive Technology, American Society for Reproductive Medicine. Assisted reproductive technology in the United States and Canada: 1993 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 1995; 64, 13–21.

54. American Fertility Society & Society of Assisted Reproductive Technology. Assisted reproductive technology in the United States and Canada: 1992 results generated from the American Fertility Society/Society for Assisted Reproductive Technology Registry. *Fertil Steril.* 1994; 62, 1121–1128.

55. Society for Assisted Reproductive Technology, American Fertility Society. Assisted reproductive technology in the United States and Canada: 1991 results from the Society for Assisted Reproductive Technology generated from the American Fertility Society Registry. *Fertil Steril.* 1993; 59, 956–962.

56. Medical Research International, Society of Assisted Reproductive Technology, American Fertility Society. *In vitro* fertilization-embryo transfer (IVF-ET) in the United States: 1990 results from the IVF-ET Registry. *Fertil Steril.* 1992; 57, 15–24.

57. Medical Research International, Society of Assisted Reproductive Technology, American Fertility Society. *In vitro* fertilization-embryo transfer (IVF-ET) in the United States: 1989 results from the IVF-ET Registry. *Fertil Steril.* 1991; 55, 14–23.

58. Medical Research International, Society of Assisted Reproductive Technology, American Fertility Society. *In vitro* fertilization-embryo transfer in the United States: 1988 results from the IVF-ET Registry. *Fertil Steril.* 1990; 53, 13–20.

59. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. *Fertil Steril.* 2012; 97, 835–842.

60. Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from *in vitro* fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med.* 2011; 8, e1000386.

61. Thapar A, Harold G, Rice F, *et al.* Do intrauterine or genetic influences explain the foetal origins of chronic disease? A novel experimental method for disentangling effects. *BMC Med Res Methodol.* 2007; 7, 25.

62. Sheffer-Mimouni G, Mashiach S, Dor J, Levran D, Seidman DS. Factors influencing the obstetric and perinatal outcome after oocyte donation. *Hum Reprod.* 2002; 17, 2636–2640.

63. Corradetti A, Talebi Chahvar S, Biondini V, Giannubilo SR, Tranquilli AL. Maternal and fetal outcomes in oocyte donor pregnancies. *Pregnancy Hypertens.* 2012; 2, 290–291.

64. Pados G, Camus M, Van Steirteghem A, Bonduelle M, Devroey P. The evolution and outcome of pregnancies from oocyte donation. *Hum Reprod.* 1994; 9, 538–542.

65. Obradors A, Rius M, Daina G, *et al.* Whole-chromosome aneuploidy analysis in human oocytes: focus on comparative genomic hybridization. *Cytogenet Genome Res.* 2011; 133, 119–126.

66. Kuliev A, Cieslak J, Verlinsky Y. Frequency and distribution of chromosome abnormalities in human oocytes. *Cytogenet Genome Res.* 2005; 111, 193–198.

67. Aye M, Di Giorgio C, De Mo M, *et al.* Assessment of the genotoxicity of three cryoprotectants used for human oocyte vitrification: dimethyl sulfoxide, ethylene glycol and propylene glycol. *Food Chem Toxicol.* 2010; 48, 1905–1912.

68. Men H, Monson RL, Parrish JJ, Rutledge JJ. Detection of DNA damage in bovine metaphase II oocytes resulting from cryopreservation. *Mol Reprod Dev.* 2003; 64, 245–250.

69. Stachowiak EM, Papis K, Kruszewski M, *et al.* Comparison of the level(s) of DNA damage using Comet assay in bovine oocytes subjected to selected vitrification methods. *Reprod Domest Anim.* 2009; 44, 653–658.

70. Malchau SS, Loft A, Larsen EC, *et al.* Perinatal outcomes in 375 children born after oocyte donation: a Danish national cohort study. *Fertil Steril.* 2013; 99, 1637–1643.