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Review

Perinatal outcomes after stimulated versus natural cycle IVF: a systematic review and meta-analysis

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KEY MESSAGE
In this systematic review and meta-analysis, a higher risk of adverse perinatal outcomes after stimulated IVF was found compared to natural or modified natural IVF, although the absolute increase in the risk may be low.

A B S T R A C T

Pregnancies resulting from assisted reproductive techniques are at higher risk of adverse perinatal outcomes compared with spontaneous conceptions. Underlying infertility and IVF procedures have been linked to adverse perinatal outcomes. It is important to know if ovarian stimulation influences perinatal outcomes after IVF. A systematic search for relevant studies was conducted up to November 2016 on the following databases: *PubMed*, *EMBASE*, *DARE* and *Cochrane Central Register of Controlled Trials*. Perinatal outcomes included preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), large for gestational age (LGA) and congenital anomalies. Data from four studies, which included a total of 96,996 and 704 singleton live births after stimulated IVF and natural or modified natural cycle IVF, were included in the meta-analysis. The risk of PTB (RR 1.27, 95% CI 1.03 to 1.58) and LBW (RR 1.95, 95% CI 1.03 to 3.67) were significantly higher after stimulated compared with natural or modified natural cycle IVF. Data from one study were available for SGA, LGA, congenital anomalies and no significant differences were reported between the groups. This study suggests a higher risk of PTB and LBW after stimulated IVF compared with natural or modified natural IVF, although the absolute increase in risk may be low.

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Introduction

Ovarian stimulation is an important part of IVF treatment. The number of oocytes retrieved has a prognostic role during IVF (Drakopoulos et al., 2016; Sunkara et al., 2011). Retrieval of three or fewer oocytes is associated with low live birth rate, and oocyte numbers up to 15 are considered optimal for maximizing live birth rate after IVF (Biljan et al., 2000; Sunkara et al., 2011).

Natural cycle IVF, devoid of any ovarian stimulation, is associated with low pregnancy rates (7–9%) per initiated cycle in unselected women (Gordon et al., 2013; Pelinck et al., 2002). The main aim of IVF, whether natural or stimulated, is to achieve a healthy live birth.

Pregnancies after IVF are at a risk of adverse perinatal outcomes compared with those conceived spontaneously (Schieve et al, 2007; Pinborg et al., 2013). This higher risk of adverse perinatal outcomes has been associated even with singleton pregnancies after IVF (McDonald et al, 2009; Pandey et al., 2012). Underlying infertility and IVF procedures, which include ovarian stimulation, in-vitro gamete handling and embryo culture, have been suggested as possible contributory factors to the adverse perinatal outcomes (Pinborg et al., 2013).

The causes of adverse perinatal outcomes associated with assisted reproductive techniques pregnancies could be multiple; however, the role of ovarian stimulation as an independent risk factor is increasingly being investigated after intrauterine insemination and IVF (Malchau et al., 2014; Pelinck et al., 2010). Earlier studies have found a high risk of low birth weight (LBW) after the use of ovarian stimulation during IVF compared with natural cycle IVF (Mak et al., 2016; Nakashima et al., 2013). A recent large cohort study, however, did not find any significant difference in the risk of preterm birth (PTB) and LBW between stimulated and unstimulated IVF (Sunkara et al., 2016). One suggested reason for the adverse perinatal outcomes with ovarian stimulation could be the effect of the resulting high oestradiol levels at the time of embryo implantation (Pereira et al., 2015). Whether ovarian stimulation itself is associated with a higher risk of the adverse perinatal outcomes, however, is unclear, and a recent study reported unequivocal results and called for a large study to address this question (Sunkara et al., 2016). We, therefore, conducted a systematic review and meta-analysis comparing perinatal outcomes after stimulated IVF versus natural or modified natural cycle IVF.

Materials and methods

Inclusion and exclusion criteria

A systematic review was conducted to identify all studies that compared perinatal outcomes after stimulated versus natural or modified natural cycle IVF. Randomized controlled trials and cohort studies were included in the review. Only cycles with fresh embryo transfer were included.

Stimulated IVF is defined as an IVF cycle involving ovarian stimulation using gonadotrophin. Natural cycle IVF involved collection of a naturally selected oocyte in a spontaneous menstrual without the use of any medication for stimulation of ovaries. Modified natural IVF cycle is defined as natural cycle IVF in which exogenous hormones or drugs are used to avoid cycle cancellation. The drugs could be gonadotrophin releasing hormone (GnRH) antagonist along with gonadotrophin add-back (Zegers-Hochschild et al., 2009). The goal of natural or modified natural cycle IVF is to use the one oocyte that spontaneously develops to dominance, and therefore these IVF cycles are associated with physiological oestradiol levels. In stimulated IVF, treatment is aimed at the development of a large number of oocytes and therefore is associated with supraphysiological oestradiol levels.

Outcomes

Outcomes were LBW, PTB, very low birth weight (very LBW), early preterm birth (early PTB), small for gestational age (SGA), large for gestational age (LGA), stillbirth rate and congenital anomaly rate after singleton live birth.

Low birth weight and very LBW are defined as birth weight less than 2500 g and 1500 g, respectively. Preterm birth and early PTB are defined as live birth before 37 weeks and 32 weeks gestation, respectively. Small for gestational age is defined as birth weight below the 10th percentile, whereas LGA is defined as birth weight above the 90th percentile. Still birth is defined as death of the fetus before birth at or after 20 weeks of gestation (Zegers-Hochschild et al., 2009).

Data search and data extraction

A systematic search was conducted using the following keywords ('Natural' OR 'Modified Natural' OR 'Unstimulated') AND ('Stimulated' OR 'Conventional') AND ('reproductive techniques, assisted'[MeSH Terms] OR 'IVF' OR 'ICSI') to identify all the potentially relevant studies published in English language from 1978 to November 2016. Searches were conducted on *PubMed/MEDLINE*, *SCOPUS/EMBASE*, *Cochrane Central Register of Controlled Trials*, *DARE*, Citation index (http://scientific.thomson.com/products/sci/) and conference abstracts in the Web of Science (http://wokinfo.com/). This was supplemented by searching the WHO international clinical trials registry and the United States NIH clinical trials registry for non-published trials along with Google search for grey literature and hand-searching the reference list of the included studies for additional studies.

Two authors (MM and MSK) independently identified the potential titles and abstracts for the eligible studies. In case of any uncertain eligibility, the full text of the study was retrieved to obtain additional information. The selection process was reported in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) diagram.

Data were extracted from eligible studies, and pre-designed forms were completed by two authors (MM and MSK) independently. Any discrepancy was resolved by consulting with a third author (SKS). For any clarification or missing data, we contacted the authors of the study.

Analysis of study bias, heterogeneity and data synthesis

We used Cochrane risk of bias tool to assess and report quality of the included randomized trial. We used the Critical Appraisal Skills Program (CASP) checklist to assess the cohort studies and assign a quality score. Two authors (MM and MSK) assessed the risk independently using standardized format and any disagreement was resolved through consensus. For categorical data, we presented the risk ratio along with 95% confidence interval and, for continuous data, we calculated the mean difference with 95% confidence interval.

We assessed the included studies for similarity across the clinical and methodological characteristics to provide a clinically meaningful result. Our inclusion criteria included observational and prospective study designs. Therefore, we used random effect model to incorporate the methodological variation into the meta analysis. We used RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) for analysis following the methods stated in the *Cochrane Handbook of systematic Reviews*. For dichotomous outcome data Mantel Hazel method and for continuous data Inverse Variance method with random effect model was used. We planned a subgroup analysis for women undergoing the following treatments: natural cycle IVF versus stimulated IVF; modified natural IVF cycle with the addition of GnRH antagonist and gonadotrophin addback versus stimulated IVF.

Assessment for heterogeneity

We assessed statistical heterogeneity by carrying out a visual inspection of the forest plot for overlapping confidence interval. The I^2 statistic was used to describe the percentage of variation across the included studies owing to heterogeneity instead of random chance. If the I^2 value was found to be over 50%, indicating a substantial heterogeneity, we used the random effects model.

Results

Search results

The systematic search (**Figure 1**), yielded 433 studies in *PubMed/MEDLINE*, 364 studies in *SCOPUS/EMBASE*, 29 studies from *Cochrane Central Register of Controlled Trials*, seven studies from *DARE* and 742 studies from citation index and web of science. The NIH clinical trials registry (ClinicalTrials.gov) and the *WHO International Clinical Trials Registry*, yielded 29 and five trials, respectively. One additional study, which was not obtained in the initial search (as the search terms were not present in the title, abstract or keywords) was obtained on hand-searching the reference list of the included studies. A total of 747 studies were obtained after excluding duplicates. After screening the title and abstract, the full text of 20 of these articles was obtained. Of these 20 studies, five studies were suitable for inclusion in this systematic review and four studies were included for quantitative data synthesis.

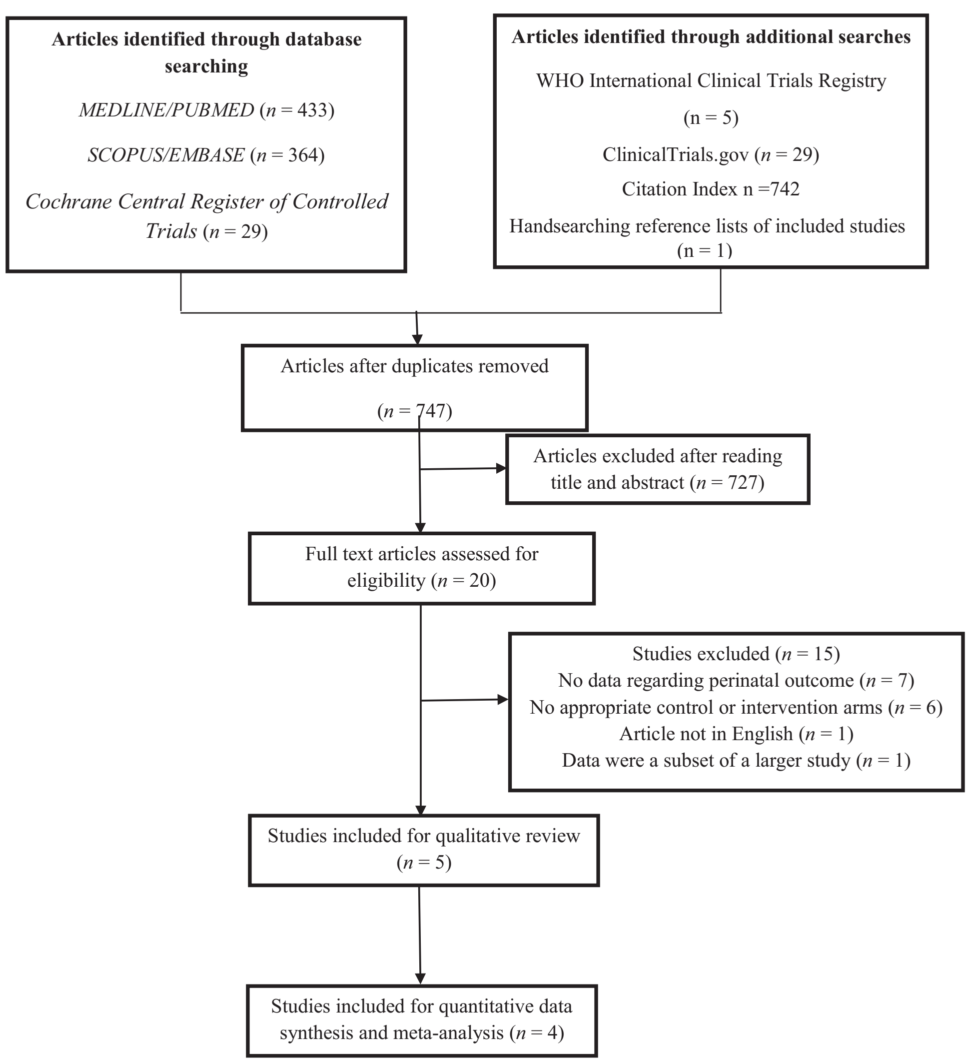

Figure 1 – PRISMA flow chart.

Characteristics of included studies

We included five studies in our review. Four were cohort studies (Mak et al., 2016; Nakashima et al., 2013; Pelinck et al., 2010; Sunkara et al., 2016), and one randomized controlled trial (Bensdorp et al., 2015) (**Table 1**).

The retrospective study by Pelinck et al. (2010) compared perinatal outcomes of 161 and 158 singleton pregnancies after fresh embryo transfers with conventional and modified natural cycle IVF. The retrospective study by Mak et al., compared perinatal outcomes of singletons after fresh conventional (*n* = 174) and modified natural cycle IVF (*n* = 190) (Mak et al., 2016). In their analysis of the Human Fertilisation and Embryology Authority data set, Sunkara et al. (2016) compared perinatal outcomes after fresh stimulated and unstimulated IVF. The study included 98,667 singletons after stimulated IVF and 262 singletons after unstimulated IVF. A randomized controlled trial by Bensdorp et al. (2015), which had three arms (conventional IVF with single embryo transfer, modified natural IVF and ovarian stimulation with intrauterine insemination) reported perinatal outcomes. Initially, single- or double-embryo transfers were carried out in the conventional IVF arm, but, after protocol amendment, only single embryo transfer was carried out. A total of 118 and 99 live births after conventional IVF and modified natural cycle IVF were reported. We obtained data for singleton live birth directly from authors.

The study by Nakashima et al. (2013) was a retrospective analysis of the Japanese assisted reproduction technique registry, and included 8224 singletons after fresh conventional IVF and 610 singletons after natural cycle IVF (Nakashima et al., 2013). The reported outcomes were LBW and mean birth weight. We could not pool the results of this study for quantitative analysis as perinatal outcomes were only available for term singletons.

All the included studies were assessed for study quality as reported in **Table 1**. The CASP score of the four included studies was 10/12 or above, indicating that these studies were of good quality. One randomized controlled trial was assessed using Cochrane risk of bias scoring, and was found to be low risk for all the domains, including risk of selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other bias (Bensdorp et al., 2015).

Results of the meta-analysis

Preterm birth

Pooling results from four studies (Bensdorp et al., 2015; Mak et al., 2016; Pelinck et al., 2010; Sunkara et al., 2016), which reported on the outcome of PTB, including 96,996 singleton live births after stimulated IVF versus 702 singleton live births after natural or modified natural cycle IVF showed a significantly higher risk of PTB with stimulated IVF (RR 1.27, 95% CI 1.03 to 1.58; I^2 0%) (**Figure 2**). If the risk of PTB in a typical clinic was 140 per 1000 singleton live births after natural or modified natural cycle IVF, then the corresponding risk of PTB will be between 144 to 221 per 1000 singleton live births after stimulated IVF (Bodemer et al., 2014).

In the subgroup analysis, the risk of PTB was significantly higher with stimulated IVF compared with the natural IVF cycle (RR 1.32, 95% CI 1.05 to 1.66; I^2 0%) (Mak et al., 2016; Sunkara et al., 2016).

Low birth weight

Pooling results from four studies (Bensdorp et al., 2015; Mak et al., 2016; Pelinck et al., 2010; Sunkara et al., 2016), which reported on the outcome of LBW, including 96,574 singleton live births after stimulated IVF versus 704 singleton live births after natural or modified natural cycle IVF, showed a significantly higher risk of LBW with stimulated IVF (RR 1.95, 95% CI 1.03 to 3.67; I^2 44%) (**Figure 3**). If the risk of LBW in a typical clinic was 41 per 1000 singleton live births after natural or modified natural cycle IVF, then the corresponding risk of LBW will be between 42 to 151 per 1000 singleton live births after stimulated IVF (Bodemer et al., 2014).

In the subgroup analysis, the risk of LBW was not significantly higher with stimulated IVF compared with the natural cycle IVF (RR 2.98, 95% CI 0.54 to 16.29; I^2 80%) (Mak et al., 2016; Sunkara et al., 2016).

Early preterm birth

Pooling results from three studies (Mak et al., 2016; Pelinck et al., 2010; Sunkara et al., 2016), which reported on the outcome of early PTB, including 96,885 singleton live births after stimulated IVF versus 608 singleton live births after natural or modified natural cycle IVF, showed a significantly higher risk of early PTB with stimulated IVF (RR 4.22, 95% CI 1.45 to 12.31; I^2 0%).

In the subgroup analysis, the risk of early PTB was significantly higher with stimulated IVF compared with the natural IVF cycle (RR 4.58, 95% CI 1.04 to 20.22; I^2 35%) (Mak et al., 2016; Sunkara et al., 2016).

Very low birth weight

Pooling results from two studies (Pelinck et al., 2010; Sunkara et al., 2016), which reported on the outcome of very LBW, including 96,289 singleton live births after stimulated IVF versus 416 singleton live births after natural or modified natural cycle IVF, showed a significantly higher risk of very LBW with stimulated IVF (RR 5.32, 95% CI 1.04 to 27.18; I^2 0%).

Small for gestational age

Only one study reported small for gestational age as an outcome, and there was no significant difference between stimulated and natural cycle IVF (3/174 [1.7%] versus 1/190 [0.53%]) (Mak et al., 2016).

Large for gestational age

Only one study reported large for gestational age as an outcome, and no significant difference was found between stimulated and natural cycle IVF (13/174 [7.5%] versus 15/190 [7.9%] (Mak et al., 2016).

Congenital anomalies

Only one study reported on congenital anomaly rates (Bensdorp et al., 2015). This study reported one case of congenital anomaly out of 111 singleton live births following stimulated IVF and four cases of congenital anomalies were noted out of 94 singletons live births after modified natural cycle IVF (0.9% versus 4.3%).

Discussion

The present study is the first systematic review evaluating the perinatal outcomes after stimulated and natural or modified natural cycle IVF. The pooled risk of perinatal outcomes, such as PTB and LBW, was significantly higher after stimulated IVF compared with natural or modified natural cycle IVF. Data from only one study was available

Table 1 – Characteristics of included studies.

Study	Study design	Time period	Stimulated IVF	Natural or modified natural IVF	Outcomes analysed	CASP score	Comments
Pelinck et al., 2010, Netherlands.	Retrospective cohort study; single IVF centre	February 2001 to April 2006	Conventional IVF GnRH agonist protocol with recombinent FSH; 161 singleton live births.	Modified natural IVF: recombinent FSH (150 IU) was added along with GnRH antagonist when dominant follicle developed; 158 singleton live births	PTB, LBW, early PTB, very LBW	10/12	Longer duration of infertility and higher proportion of women smoking noted in the conventional IVF arm.
Mak et al., 2016, USA	Retrospective cohort study; single IVF centre	2007 to 2013	Conventional IVF GnRH agonist or antagonist protocol with gonadotrophin; 174 singleton live births	Natural cycle IVF; no GnRH antagonist or FSH used, HCG trigger given; 190 singleton live births	PTB, LBW, early PTB, SGA, LGA	11/12	Women in natural cycle IVF were older. More women with polycystic ovary syndrome, higher numbers of embryos transferred and more blastocyst transfers in the stimulated IVF arm.
Sunkara et al. 2016, UK	Retrospective cohort study; HFEA database	1991 to 2011	Stimulated IVF; 98,667 singleton live births	Unstimulated IVF; 262 singleton live births	PTB, LBW, early PTB, very LBW	11.5/12	Information on body mass index, comorbid medical conditions or smoking status was not available.
Nakashima et al. 2013, Japan	Retrospective cohort study; Japanese registry.	2007to 2008	Ovarian stimulation with clomiphene citrate, clomiphene citrate with gonadotrophin, agonist or antagonist protocol; 8224 singleton live births	Natural cycle IVF with no ovarian stimulation; 610 singleton live births	LBW	10/12	Only term births included in this study. Hence not included for quantitative data synthesis
Bensdorp et al. 2015, the Netherlands	Multi-centre randomized controlled trial.	January 2009 to February 2013	Conventional IVF with recombinent FSH (150 IU) GnRH agonist or antagonist protocol and single embryo transfer; 118 singleton live births	Modified natural IVF: recombinent FSH (150 IU) was added along with GnRH antagonist when dominant follicle developed. 99 singleton live births	PTB, LBW, congenital anomalies	Risk of bias: all domains low risk	Multi-centre, open label, non-inferiority randomized controlled trial.

CASP, Critical Appraisal Akills Program; HFEA, Human Fertilization and Embryology Authority; LBW, low birth weight; PTB, preterm birth.

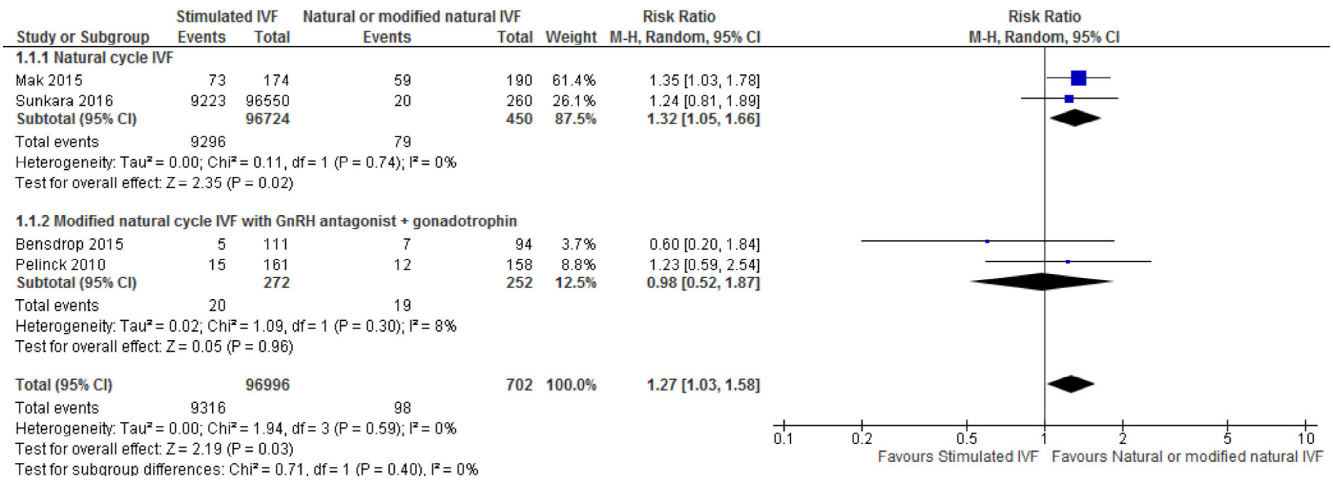

Figure 2 – Preterm birth: stimulated versus natural or modified natural IVF.

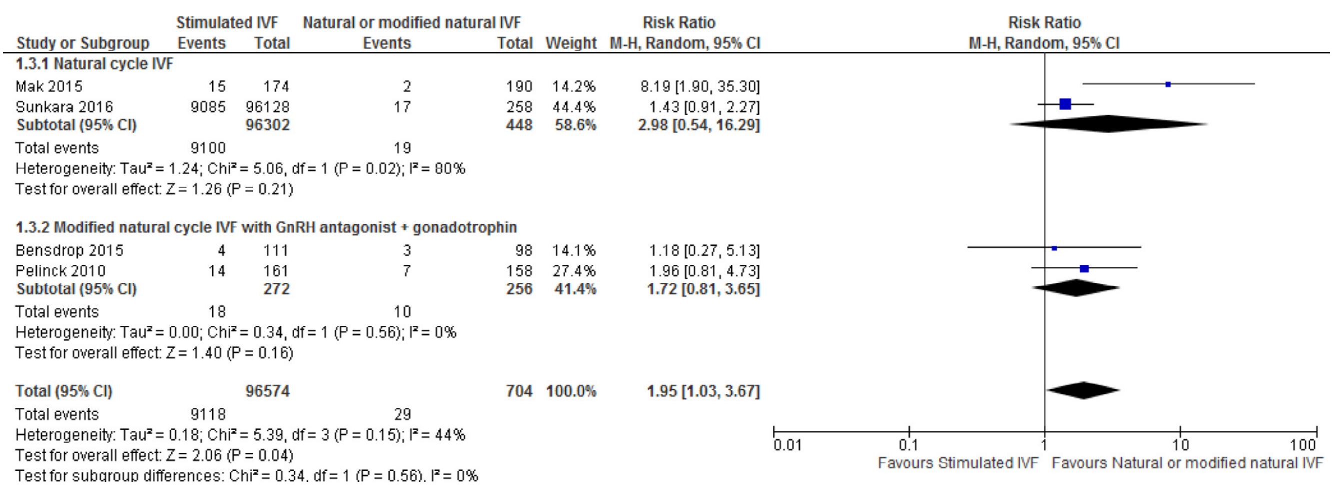

Figure 3 – Low birth weight: stimulated versus natural or modified natural IVF.

for SGA, LGA, congenital anomalies, and no significant differences were reported between the two groups.

Quality of evidence

Of the five studies included in the review, two consisted of large datasets from national registries (Nakashima et al., 2013; Sunkara et al., 2016), and one was a high-quality randomized trial (Bensdorp et al., 2015). The combined pooled analysis of 97,700 IVF singleton live births makes it the largest study to date. The review included one high-quality RCT (Bensdorp et al., 2015) and cohort studies with CASP scores ranging from 10 to 11.5 (Mak et al., 2016; Nakashima et al., 2013; Pelinck et al., 2010; Sunkara et al., 2016).

We included only singleton live births owing to the confounding effect of multiple birth on perinatal outcomes. We also excluded frozen cycles because of its association with higher birth weight and macrosomia, which may affect the true estimates (Maheshwari et al., 2016).

Limitations

We could not carry out age-adjusted comparison, although, in the largest included study, perinatal outcomes were adjusted for age (Sunkara et al., 2016). Transfer of more than one embryo in many cases after stimulated IVF may have resulted in vanishing twin pregnancies and consequently confounded perinatal outcomes (Evron et al., 2015). Another confounder for which adjusted comparison could not be carried out was duration of infertility (Messerlian et al., 2013). A recent study has suggested increased risk of adverse perinatal outcomes in the case of over 20 oocytes retrieved during IVF (Sunkara et al., 2015), and a proportion of such cases with high oocyte yield in the stimulated IVF group may be a potential confounder.

Agreement with other reviews and studies

This is the first systematic review evaluating the perinatal outcomes after stimulated and natural or modified natural cycle IVF. A large study based on data from Japanese birth registry compared the birth weight after different assisted reproduction technique procedures, and found a two-fold increase in risk of LBW aftrer ovarian stimulation compared with natural cycle IVF (Nakashima et al., 2013). The risk of LBW was significantly higher after stimulated IVF using GnRH agonist (aOR 1.72, 95% CI 1.17 to 2.62) and stimulated IVF using GnRH antagonist (aOR1.60, 95% CI 1.05 to 2.50) compared with natural IVF (Nakashima et al., 2013).

The largest included study in our review analysed a retrospective dataset spanning 2 decades from the Human Fertilisation and Embryology Authority, and found no significant difference in PTB (9.6% versus 7.7%; aOR 1.43, 95% CI 0.91 to 2.26) and LBW (9.5% versus 6.6%; aOR 1.58, 95% CI 0.96 to 2.58) after stimulated and unstimulated IVF (Sunkara et al., 2016), which is contrary to the findings of the present study. Although the difference did not reach statistical significance, the smaller number of events in unstimulated group led to wider confidence intervals. In the current meta-analysis, pooling of additional studies resulted in pooled estimate with a narrower confidence interval for main perinatal outcomes which is more likely to be closer to true estimate.

Biological plausibility

Although infertility is considered an independent risk factor for adverse perinatal outcomes, ovarian stimulation and IVF methods may have a contributory role to play. Earlier studies have reported that supraphysiological levels of oestradiol during ovarian stimulation may be associated with higher risk of pre-eclampsia and adverse perinatal outcomes (Imudia et al., 2012; Pereira et al., 2015, 2017). Another study suggested a link between supraphysiological hormonal environment and impaired trophoblast differentiation, resulting in abnormal placentation (Mainigi et al., 2014). The findings of the present study (increased risk of PTB and LBW after stimulated IVF compared with natural cycle IVF) further strengthen the suggested link between ovarian stimulation and adverse perinatal outcomes. Although the absolute increase in risk for LBW may be low, as perinatal outcomes are associated with future health implications such as adult onset cardiovascular diseases, there is a need to further investigate and validate these findings (Mercuro et al., 2013).

In conclusion, the risk for PTB and LBW were significantly higher after stimulated IVF compared with natural or modified cycle IVF, although the absolute increase in the risk may be low.

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