Which is better for mothers and babies, fresh or frozen thawed blastocyst transfer?

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Abstract

Background: In recent years, there have been emerging many reports on the pregnancy outcomes of fresh blastocyst transfer (BT) and freeze-thaw BT, but these conclusions are controversial and incomplete. To compare the pregnancy outcomes, maternal complications and neonatal outcomes of fresh and frozen-thawed BT in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) cycles, we conducted a meta-analysis.

Methods: A meta-analysis was conducted by searching PubMed, Embase, and Cochrane Library until January 2020. Data were extracted independently by two authors.

Results: 42 studies, including 12 randomized controlled trials (RCT) met the inclusion criteria. Fresh BT showed lower implantation rate (IR), pregnancy rate (PR), ongoing pregnancy rate (OPR) and higher eptopic pregnancy rate (EPR) compared with frozen-thawed BT consistent with the results of RCT. The risks of moderate or severe ovarian hyperstimulation syndrome (OHSS), placental abruption (PA) and preterm were higher in fresh BT than in the frozen-thawed BT. The risk of pregnancy-induced hypertension (PIH) and pre-eclampsia was decreased in fresh BT, however, no significant differences of risks for PIH, pre-eclampsia, OHSS, and preterm was found between the two group in the 2 RCT included. Compared with frozen-thawed BT, fresh BT appears to be associated with small for gestational age (SGA) and low birth weight (LBW). No differences in the incidences of neonatal mortality and neonatal malformations were observed between fresh and frozen-thawed BT.

Conclusions: In summary, Considering the higher IR, PR, OPR, lower EPR, and the decreased risks of OHSS, PA and preterm, as well as the incidences of SGA and LBW in frozen-thawed BT, this meta-analysis indicates that frozen-thawed BT may be a better choice for mothers and babies compared with fresh BT.

Key words: Fresh blastocyst transfer, frozen thawed blastocyst transfer, pregnancy outcome, maternal complications, neonatal outcomes

Background

As cryopreservation technology develops during the past few decades, the proportion of frozen blastocyst transfer (BT) has increased [1]. There have been concerns about the impact of cryopreservation on the pregnancy outcomes, maternal complications and health of born children [2]. A few studies have compared the pregnancy outcomes following fresh BT and cryopreserved-thawed BT in patients undergoing IVF/ICSI cycles [3–5]. However, the findings are controversial. A recent meta-analysis study supported the hypothesis that single cryopreserved BT might not be the best choice compared with single fresh BT in patients undergoing IVF/ICSI cycles [3]. However, another systematic review and meta-analysis study suggest that the pregnancy outcomes may be improved by performing frozen-thawed BT [4].

With regard to maternal complications, Maheshwari et al showed that frozen-thawed BT was associated with decreased risks of postpartum hemorrhage (PH), placental abruption (PA) and placenta previa (PP) and preterm compared with fresh BT, and the pregnancies arising from frozen-thawed BT seem to have lower risks of maternal complications [2]. Shavit et al reached at the opposite conclusion that frozen-thawed BT may contribute to increased risk of maternal complications such as pre-eclampsia and gestational diabetes mellitus (GDM) [6]. The latest randomized controlled trial reported that the incidence of pre-eclampsia was higher after frozen-thawed BT than fresh BT, and the risk of moderate or severe ovarian hyperstimulation syndrome (OHSS) was similar in both groups [7].

Considering the neonatal outcomes, an early review demonstrated that there were no significant differences in incidences of perinatal death, low birth weight of infants between fresh BT and frozen-thawed BT [8]. However, another review suggested that the incidences of small for gestational age (SGA), low birth weight (LBW), and perinatal mortality were lower in women who received frozen thawed BT [2].

There is growing concern on whether children born after frozen thawed BT have increased risks of congenital malformations compared to that after fresh BT in IVF/ICSI cycles. A register-based cohort study suggested that the risk for congenital
malformation of the children born after frozen thawed BT was not increased compared with fresh BT, in addition, no increased risks concerning the affected organ system were found between the two groups [9].

Due to the limited sample size, the past meta-analysis conclusions were controversial. With the emergence of new reports, there is an urgent need to perform a meta-analysis to compare the multiple outcomes following fresh BT and frozen-thawed BT to provide guidance for clinical practice. The purpose of this meta-analysis was to examine the pregnancy outcomes, maternal complications and neonatal malformations after frozen thawed BT versus fresh BT in an IVF/ICSI cycle and assess if the frozen thawed BT is a better choice than fresh BT.

Methods

Search strategy

We searched the published articles in PubMed, EMBASE and Cochrane Library databases up to August 2019, using the following terms as key words: 'humans', 'embryo*', 'cryo*', 'frozen', 'vitrif*', 'freez*', and 'fresh'. A comprehensive search strategy for MEDLINE was presented in Appendices.

Eligibility Criteria and Data Extraction

We included trials comparing clinical outcomes between patients undergoing IVF/ICSI cycles with fresh or frozen BT. Two researchers assessed the eligibility of studies and extracted the data independently. Any disagreement was resolved by discussion. Study characteristics and outcome data were generated from forty-two eligible studies.

Risk of Bias Assessment

We assessed the risk of bias from included studies following the guidance suggested by the Cochrane Collaboration, regarding the generation of sequence allocation, allocation concealment, blinding, and incomplete outcome data for each trial included in the review. Funnel plots were adopted to investigate whether the difference was due to publication or reporting bias.

Outcome Measures

The pregnancy outcome: Implantation rate reflected the number of gestational sacs seen per embryo transferred. Pregnancy was identified through increased serum hCG level within 10 days after blastocyst transfer. Ongoing pregnancy was defined as pregnancy proceeding beyond the 10th gestational week. Clinical pregnancy was considered as the presence of a gestational sac with fetal heart activity, as assessed by ultrasound at 7 weeks of gestation. Miscarriage included any pregnancy that did not become ongoing pregnancies. Multiple pregnancy was defined as a gestation with more than one fetus. Live birth was calculated by birthing events per embryo transfer. We recorded the following maternal complications: GDM, pregnancy-induced hypertension (PIH) and pre-eclampsia, moderate or severe OHSS, preterm, PP, PA, PH and preterm rupture of membrane. Preterm was defined as live births < 37 weeks' gestational age. Very preterm was defined as live births < 32 weeks' gestational age. The neonatal outcomes included gestational age at delivery, birth weight, stillbirth, perinatal mortality and neonatal mortality. Large for gestational age (LGA) was defined as birthweight higher than the 90th percentile of referential birthweight. SGA was defined as birthweight lower than the 10th percentile of referential birthweight. Very small for gestational age (VSGA) was defined as weighing below the 3rd percentile of referential birthweight. High birth weight baby (HBW) was defined as weight of > 4000 g at birth. Very high birth weight baby (VHBW) was defined as weight of > 4500 g at birth. Low birth weight baby (LBW) was defined as weight of < 2500 g at birth. Very low birth weight baby (VLBW) was defined as weight of < 1500 g at birth. We also analyzed the neonatal malformations including congenital anomaly and chromosomal aberrations, different organ system malformations.

Statistical analysis
All statistical analysis was conducted using Rev Man software. For the included studies, the dichotomous data results for each of the studies eligible for meta-analysis were expressed as a risk ratio (RR) with 95% confidence intervals (CI). These results were combined for meta-analysis with use of the Mantel/Haenszel model along with the random effects model. Statistical heterogeneity was assessed with a chi-squared test and quantified with the I^2 statistic. An I^2 value greater than 50% may be considered to represent substantial heterogeneity. p < 0.05 was considered statistically significant.

Results

A total of 3645 available publications were retrieved in our search. Of these, 3473 were excluded after reading the title and the abstract. Finally, 42 articles, including 12 randomized controlled trials (RCT) and 30 non-randomized controlled trials (NRCT) were considered to be eligible by one or both reviewers (Supplemental Fig. 1). Table 1 gives the details of all included studies.

Pregnancy outcomes

Total 12 trials reported that implantation rate (IR) decreased in the fresh BT compared with frozen-thawed BT group (RR 0.81, 95% CI 0.70–0.94, P = .006, Heterogeneity: I^2 = 85%) consistent with the results of RCT (RR 0.79, 95% CI 0.70–0.90, P = .0004, Heterogeneity: I^2 = 65%) (Fig. 1A). 12 trials were included in this comparison of the pregnancy rate (PR) in the fresh BT and frozen-thawed BT (Fig. 1B). When the PR were compared with frozen-thawed BTs, the fresh BT showed a lower pregnancy rate (RR 0.84, 95% CI 0.74–0.95, P = .005, Heterogeneity: I^2 = 88%) consistent with the results of RCT (RR 0.83, 95% CI 0.78–0.89, P < .00001, Heterogeneity: I^2 = 0%). 13 trials investigated the effect of fresh BT and frozen-thawed BT on ongoing pregnancy rate (OPR) (Fig. 2A). Compared with women who had frozen-thawed BT, women who underwent fresh BT showed a decreased OPR (RR 0.78, 95% CI 0.66–0.92, P = .004, Heterogeneity: I^2 = 91%), in good agreement with the results of RCT (RR 0.80, 95% CI 0.75–0.87, P < .00001, Heterogeneity: I^2 = 0%). The above results indicate that the frozen-thawed BT tends to result in higher IR, PR, and OPR. 12 trials showed that the fresh BT resulted in a statistically significant increase in the ectopic pregnancy rate (EPR) compared with the frozen-thawed BT (RR 1.60, 95% CI 1.05–2.43, P = .001, Heterogeneity: I^2 = 65%), which was coincidence with the results of RCT (RR 1.96, 95% CI 1.27–3.01, P = .002, Heterogeneity: I^2 = 0%) (Fig. 2B). The clinical pregnancy rate (CPR) (RR 0.99, 95% CI 0.87–1.13, P = .85, Heterogeneity: I^2 = 95%), miscarriage rate (MR) (RR 0.87, 95% CI 0.75–1.00, P = .05, Heterogeneity: I^2 = 76%), the multiple pregnancy rate (MPR) (RR 0.93, 95% CI 0.69–1.24, P = .61, Heterogeneity: I^2 = 59%) and the live birth rate (LBR) (RR 1.05, 95% CI 0.92–1.20, P = .47, Heterogeneity: I^2 = 92%) showed no statistically significant differences between the two groups (Supplemental Fig. 2 and Supplemental Fig. 3). According to RCT, CPR decreased in the fresh BT compared with frozen-thawed BT group (RR 0.86, 95% CI 0.75–1.00, P = .04, Heterogeneity: I^2 = 56%), while MR (RR 0.86, 95% CI 0.65–1.13, P = .27, Heterogeneity: I^2 = 37%), MPR (RR 0.92, 95% CI 0.70–1.21, P = .56, Heterogeneity: I^2 = 30%) and LBR (RR 0.92, 95% CI 0.75–1.12, P = .41, Heterogeneity: I^2 = 87%) showed no statistically significant differences. In conclusion, our meta-analysis showed that fresh BT showed lower IR, PR, OPR and higher EPR than frozen-thawed BT. There were no differences observed in the MR, MPR and LBR between the fresh and frozen-thawed BT.

Maternal complications

To investigate whether fresh BT or frozen-thawed BT has any effect on maternal complications, we compared the incidence of PIH and pre-eclampsia, OHSS, preterm, GDM, PP, PA, PH, preterm rupture of membrane between the two groups. Lower incidences of PIH and pre-eclampsia were observed in fresh BT when being compared with frozen-thawed BT (RR 0.57, 95% CI 0.43–0.75; P < .0001, Heterogeneity: I^2 = 32%) (Fig. 3A). According to 6 trials, the risk of OHSS was higher in fresh BT than in frozen-thawed BT (RR 3.41, 95% CI 1.72–6.77; P = .0005, Heterogeneity: I^2 = 23%) (Fig. 3B). Likewise, women who underwent fresh BT showed an increase risk of PA (RR 1.67, 95% CI 1.14–2.46; P = .009, Heterogeneity: I^2 = 0%) (Fig. 4A). Compared with the frozen thawed BT group, the fresh group with higher risks of preterm (RR 1.15, 95% CI 1.04–1.27, P = .006, Heterogeneity: I^2 = 64%) (Fig. 4B) and very preterm (RR 1.29, 95% CI 1.09–1.54, P = .004, Heterogeneity: I^2 = 32%) (Supplemental Fig. 4A). However, according to 2 RCT, we found that there was no statistically difference in PIH and pre-
eclampsia (RR 0.82, 95% CI 0.31–2.15; P = .68, Heterogeneity: $I^2 = 65\%$), OHSS (RR 1.84, 95% CI 0.73–4.63; P = .19, Heterogeneity: $I^2 = 0\%$), preterm (RR 0.79, 95% CI 0.42–1.48; P = .46, Heterogeneity: $I^2 = 53\%$) between fresh BT and frozen-thawed BT.

The incidence of GDM (RR 0.79, 95% CI 0.56–1.12; P = .19, Heterogeneity: $I^2 = 16\%$) in line with the results of RCT (RR 0.86, 95% CI 0.59–1.25; P = .42, Heterogeneity: $I^2 = 0\%$), PP (RR 1.24, 95% CI 0.92–1.66, P = .16, Heterogeneity: $I^2 = 30\%$) and PH (RR 1.48, 95% CI 0.91–2.40; P = .11, Heterogeneity: $I^2 = 60\%$) (Supplemental Fig. 4B-D) did not statistically differ between fresh BT groups and frozen-thawed BT groups. Only one study compared the incidence of preterm rupture of membrane between the fresh BT and the frozen-thawed BT group, reporting a slightly lower rate in the former (5.3% vs. 5.9%) [7]. In summary, hypertension and pre-eclampsia in fresh BT is decreased compared to in frozen-thawed BT, while the risks of OHSS, PA and preterm in fresh BT are higher than in the frozen-thawed BT. However, the two groups have similar incidence of GDM, PP and PH.

**Neonatal outcomes**

8 studies compared the LGA rate between fresh and frozen-thawed BT (Fig. 5A). The LGA rate of the fresh BT group was lower (RR 0.65, 95% CI 0.62–0.69, P < .00001, Heterogeneity: $I^2 = 0\%$). However, the SGA rate of the fresh BT was higher than that of the frozen-thawed BT group according to the data from 8 studies included (RR 1.59, 95% CI 1.47–1.73, P < .00001, Heterogeneity: $I^2 = 0\%$) (Fig. 5B). The RR of HBW (RR 0.59 95% CI 0.57–0.61, P < .00001, Heterogeneity: $I^2 = 0\%$) (Fig. 5C) and VHBW (RR 0.51, 95% CI 0.36–0.71, P < .0001, Heterogeneity: $I^2 = 16\%$) (Supplemental Fig. 5A) in fresh BT showed an absolute decrease when compared with frozen thawed BT group in the light of the results from these 4 trials. On the contrary, the LBW (RR 1.43, 95% CI 1.33–1.54, P < .00001, Heterogeneity: $I^2 = 47\%$) (Fig. 4D) and VLBW (RR 1.32, 95% CI 1.16–1.50, P < .0001, Heterogeneity: $I^2 = 12\%$) (Supplemental Fig. 5B) in fresh BT shows an absolute increase when compared with frozen thawed BT. In addition, we also investigated the stillbirth, perinatal mortality and neonatal mortality between the two groups (Supplemental Fig. 5C-E), and no significant differences were found between them.

In conclusion, fresh BT tends to lead to SGA and LBW. Frozen thawed BT has the opposite effect. The stillbirth, perinatal mortality and neonatal mortality showed no statistically significant differences between the two groups.

**Neonatal malformations**

From the data we have summarized, no risk differences in congenital anomaly and chromosomal aberration rates of newborns were detected between fresh BT and frozen-thawed BT (RR 1.06 95% CI 0.97–1.15, P = .19 Heterogeneity: $I^2 = 0\%$) (Fig. 6A). Further inspecting the risk of the different organ system malformations in newborns including circulatory system (Fig. 6B), respiratory system (Fig. 6C), nervous system (Fig. 6D), gastrointestinal system (Supplemental Fig. 6A), genitourinary system (Supplemental Fig. 6B), eye, ear, face (Supplemental Fig. 6C), and musculoskeletal system (Supplemental Fig. 6D), no increased risk in frozen-thawed BT were found. The above data indicate that freeze-thaw BT is not a risk factor for neonatal malformations.

**Discussion**

Great advances have been made in cryopreservation culture technique for embryo since the success of the first pregnancy of frozen-thawed embryo transfer (FET) in 1983 [10]. This technique has been applied as a supplement to IVF and embryo transfer. FET was accepted by every center and has become an essential part of IVF/ICSI treatment. Therefore, the increased use of FET has intensified the awareness of the safety of the technique [11]. The meta-analysis compared the outcomes of fresh BT and frozen-thawed BT undergoing IVF/ICSI cycles, with comprehensive respects of the pregnancy outcomes, maternal complications, neonatal outcomes and malformations.

With respect to pregnancy outcomes, our study showed that frozen BT was associated with increased IR, PR and OPR and a decreased EPR compared with fresh thawed BT, which was consistent with the results of RCT. There was no difference in
CPR, MR, MPR, and LBR. However, according to RCT, no difference in MR, MPR and LBR and a decreased CPR were tested in fresh BT compared with fresh thawed BT. Recently, Zeng et al. showed that there was no difference in IR, CPR, MR, and MPR, but an increased LBR was found in fresh BT comparing with cryopreserved thawed BT [3]. Roque et al. showed frozen-thawed BT significantly improved CPR and OPR in patients in IVF/ICSI cycles [4]. The incidence of EP between the two groups varied in different studies. The inconsistent conclusions may be related to differences in the data included. A previous study reported that EPR was higher in frozen thawed BT [12]. However, our study suggested that frozen thawed BT was related to lower EPR consistent with these studies [13, 14]. However, in these reports sub-category analysis wasn't performed according to the stage of embryo transfer including cleavage and blastocyst stage embryos. Hence, in view of the increased IR, PR, OPR and decreased EPR following frozen thawed BT, we believe that frozen thawed BT have a better pregnancy outcome than fresh BT. Embryo implantation is one of the important steps for reproductive success, and implantation failure remains an unsolved problem in IVF/ICSI cycles. The primary responsible cause of failure is the impairment of the endometrial receptivity (ER), whereas the embryo itself is responsible for the failure [15]. A study suggested impaired ER is more apt to occur in fresh ET cycles after ovarian stimulation, when compared with FET cycles with artificial endometrial preparation. Impaired ER apparently accounted for most implantation failures in the fresh group [16]. The another explanation for better results in pregnancies subsequent to frozen BT is that the physical effects of freezing and thawing embryos may filter out weaker embryos and allow only good quality ones to survive, resulting in better fetal growth [17].

From the perspective of maternal complications, our research demonstrated that the risks of OHSS, PA and preterm in fresh BT are increased compared to in frozen-thawed BT. On the contrary, the risk of PIH and pre-eclampsia in fresh BT is decreased compared to in frozen-thawed BT. According to 2 RCT, no difference in PIH and pre-eclampsia, OHSS and preterm were found between fresh BT and frozen-thawed BT. Owing to the few numbers of RCT reporting maternal complications, the insufficient evidence may lead to inconsistent results. There were no difference in the GDM and PP of the fresh and cryopreserved-thawed BT. OHSS is an iatrogenic condition resulting from an excessive ovarian response to superovulation medication. According to a previous meta-analysis, no difference was found in OHSS between fresh BT and frozen thawed BT [18]. However, the previous data were insufficient. A few recent reviews demonstrated that singleton pregnancies after transfer of frozen thawed embryos were associated with lower risks of preterm birth (<37 weeks), very preterm birth (<32 weeks) when compared with those after fresh embryos transfer, which agrees with our research [2, 19, 20].

In regard to neonatal outcomes, our study suggested that there were lower risks of SGA, LBW in singleton pregnancies after frozen thawed BT compared with fresh BT, which was consistent with the previous meta-analysis [2]. However, the stillbirth, and perinatal mortality neonatal mortality is not statically different between two groups. Moreover, with respect of neonatal malformations, there was no difference between fresh BT and frozen thawed BT. In conclusion, singleton pregnancies after frozen thawed BT seem to have better neonatal outcomes than those after fresh BT, owing to lower risks of SGA and LBW. The reasons for better neonatal outcomes of frozen BT compared with fresh BT are not known yet. In contrast to IVF with fresh embryo transfer, FET is usually performed in minimally stimulated or natural cycles. This lowers the risk of SGA and LBW after FET, which may attribute to a luteal phase that mirrors the natural cycle, with favorable effects on the endometrium and early implantation [20]. Another probable explanation was that controlled ovarian hyperstimulation (COH) was associated with poorer neonatal outcomes assessed by SGA and LBW in a rent study [21]. The results favoring frozen thawed BT instead of fresh BT may relate to the adverse effects of COH on ER [22, 23]. Therefore, elective cryopreservation of viable embryos could be an alternative to avoid the deleterious effects of COH in embryo endometrium synchrony [16, 24].

**Strengths and limitations**

The major strength of this systematic review is the comprehensive literature search, identifying study objects from a huge number of relevant publications; another strength is the many aspects of pregnancy outcomes, maternal complications and neonatal outcomes the study evaluated between frozen or fresh BT to know which is better for mothers and babies. In addition, we conducted RCT and NRCT meta-analysis respectively to improve the quality of evidences. But the present meta-analysis also has some limitations; one of which was the significant heterogeneity about the pregnancy outcome in the meta-analysis. We tried to find the source of heterogeneity by running a subgroup analysis to examine the source of heterogeneity.
but failed. Besides, the baseline characteristics of patients differ more or less among the included studies, including countries, age, smoking, duration of infertility, type of infertility, endometrial thickness, and cryopreservation type.

**Conclusion**

In summary, considering the higher IR, PR, OPR, lower EPR, and the decreased risks of OHSS, PA and preterm, as well as the incidences of SGA and LBW in frozen-thawed BT, this meta-analysis indicates that frozen-thawed BT may be a better choice for mothers and babies in IVF/ICSI cycles compared with fresh BT.

**List Of Abbreviations**

BT: blastocyst transfer; PH: postpartum hemorrhage; PA: placental abruption; PP: placenta previa; GDM: gestational diabetes mellitus; OHSS: ovarian hyperstimulation syndrome; SGA: small for gestational age; LBW: low birth weight; PIH: pregnancy-induced hypertension; LGA: large for gestational age; VSGA: Very small for gestational age; HBW: High birth weight baby; VHBW: Very high birth weight baby (VHBW); RR: risk ratio; CI: confidence intervals; RCT: randomized controlled trials; NRCT: non-randomized controlled trials. IR: implantation rate; PR: pregnancy rate; OPR: ongoing pregnancy rate; EPR: ectopic pregnancy rate; LBR: live birth rate; MR: miscarriage; MPR: multiple pregnancy rate

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

XZ* and MY conceived and designed the review. XZ* carried out activities from inception to the draft of the manuscript and is the guarantor of the review. XZ* and MY developed the search strings, selection, analysis and interpretation. XZ*, MY, LL, CS, TL, LC, WG, YM and YW rigorously review the manuscript. All authors read and approved the final version of the manuscript.

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Table
| Author Year          | Patients                                                                 | Age (fresh/frozen)       | Numbers of patient (fresh/frozen) | Design               | Duration of trial | Outcomes                                      |
|----------------------|--------------------------------------------------------------------------|--------------------------|-----------------------------------|----------------------|-------------------|-----------------------------------------------|
| Aflatoonian 2010a    | Patients who were classified as high responders                          | 28.1±3.5/27.3 ±4.4      | 187/187                           | Prospective RCT      | Feb 2007 to Feb 2009 | IR, CPR, MR, MPR, OPR                         |
| Aflatoonian 2010b    | Pregnancies after fresh ET vs. frozen ET                                  | 29.9±4.7/30.4±4.5       | 500/200                           | Prospective RCT      | Mar 2006 to Mar 2008 | MR, LBR, PR, EPR, Preterm, LBW, Neonatal mortality |
| Aghahosseini 2017    | Infertile women with a progesterone level ≥1.8ng/dl                      | 32.8±5.8/30.5±4.7       | 36/36                             | RCT                  | Jan to Apr 2016 | CPR, MR, LBR, PR                              |
| Belva 2008           | All pregnancies after transfer of frozen-thawed embryos obtained by conventional IVF or ICSI | No statement            | 6402/1351                         | Unmatched cohort study | No statement | MR, MPR, LBR, OPR, PR, EPR, LBW, Stillbirth |
| Bourdon 2018         | Women with endometriosis infertile                                       | 34.3±3.9/34.3 ±4.1      | 135/135                           | Retrospective matched cohort study | Oct 2012 to Dec 2014 | LBR, MPR, OPR |
| Chen 2016            | Infertile women with PCOS                                                | 28.2±3.1/28.1 ±3.0      | 762/746                           | Retrospective matched cohort study | Jun 2013 to May 2015 | CPR, MR, LBR, OPR, OHSS, Preterm, PIH, Stillbirth |
| Coates 2017          | Patients undergoing IVF treatment using preimplantation genetic screening | 36.6(25–42)/36.7(27–42) | 88/91                             | RCT                  | Dec 2013 to Aug 2015 | IR, MPR, LBR, OPR |
| Eum 2016             | Women who underwent the transfer of one or two fresh or vitrified-warmed blastocysts | Using a cutoff of 35 years | 69/206                             | Retrospective study  | Jan 2013 to Dec 2014 | IR, CPR, MR, LBR, MPR |
| Fauque 2010          | Women with adequate ovarian function                                      | < 36 years               | No statement                      | Prospective nonrandomized study | 2005 to 2007 | CPR, MR, LBR, MPR, EPR |
| Feng 2012            | Women with various infertile causes                                      | 31.02±3.69/31.60±3.56   | 604/ 384 (252/142 singletons)     | Retrospective study  | Jan 2009 to Dec 2010 | IR, CPR, MR, LBR, MPR, EPR, Preterm, LBW, Stillbirth, Neonatal malformations |
| Study | Research Question | Patients at Risk | No. Patients | Study Design | Baseline | Year of Study | Outcomes |
|-------|------------------|-----------------|-------------|-------------|-----------|--------------|----------|
| Ferraretti 1999 [34] | Patients at risk of OHSS | 31.46±2.4/31.66±2.8 | 67/58 | Prospective RCT | Jan 1996 to Jul 1997 | CPR, LBR, PR, OHSS |
| Healy 2010 [35] | Women with singleton births in Victoria Australia | No statement | 4058/2045 | Retrospective cohort study | 1991 to 2004 | PP, PA, PH |
| Henningsen 2011 [36] | Women treated with ART who had given birth to a singleton after IVF, ICSI, or FER | No statement | 716/716 (singleton) | Retrospective cohort study | 1994 to 2008 | LBW |
| Henman 2005 [37] | Patients with three or more usable blastocysts | <38 years | 121/156 | Prospective study | Apr 2000 to Dec 2001 | IR, CPR, LBR, MPR |
| Ishihara 2014 [38] | Undergoing single embryo transfer cycles | Any age | 33,559/118866 (5,981/27408 singletons) | Retrospective study | 2008 to 2010 | CPR, MPR, EPR, PP, PA, PIH, LGA, SGA, LBW, HBW, Stillbirth |
| Korosec 2007 [39] | Women within their first three treatment cycles | <37 years | 65/214 | Prospective study | Apr 2004 to Jun 2006 | CPR |
| Le 2018 [40] | Non-PCOS women undergoing IVF/ICSI | Any age | 391/391 | RCT | Jun to Apr 2015 | MR, LBR, EPR, GDM, PIH |
| Magdi 2017 [41] | Women with recurrent implantation failure | <38 years | 90/81 | Prospective cohort study | Apr 2014 to Oct 2016 | IR, CPR, MR, MPR, OPR, PR |
| Maheshwari 2016 [42] | Singleton births after IVF/ICSI in the UK | Any age | 95111/16521 (singletons) | Retrospective cohort study | 1991 to 2011 | Preterm, LBW, HBW, Neonatal malformations |
| Martikainen 2001 [43] | Women with at least four good quality embryos after IVF/ICSI | No statement | 74/74 | RCT | No statement | CPR, MR, LBR, EPR |
| Martikainen 2004 [44] | Women in the first or second treatment cycle when a top-quality embryo is available | <36 years | 308/311 | Retrospective cohort study | 2000 to 2002 | CPR, MR, MPR, LBR, OPR, EPR |
| Pelkonen 2010 [45] | The registers of two infertility outpatient clinics, two university hospitals and the Finnish Medical Birth Register | Any age | 3298/1852 (2942/1830 singleton) | Unmatched cohort study | 1995 to 2006 | PP, PA, PH, Preterm, LBW, SGA, Stillbirth |
| Pelkonen 2014 [9] | Women who have | Any age | 2942/1830 (Singleton) | Register-based cohort study | 1995 to 2006 | Major congenital |
| Authors | Description | Ages | Study Type | Study Dates | Outcomes |
|---------|-------------|------|------------|-------------|----------|
| Pelkonen 2015 [46] | Women who had undergone ART treatments leading to singleton live births | Any age | Register-based cohort study | 1995 to 2006. | Preterm, LGA, SGA, LBW, Neonatal malformations |
| Pinborg 2010 [47] | All singletons who according to the Danish IVF Register | Any age | Retrospective cohort study | 1995 to 2007 | LBW, Preterm, Stillbirth, Neonatal malformations |
| Roy 2014 [48] | Infertile patients who underwent fresh or vitrified-warmed embryo transfers. | No statement | Retrospective study. | Mar 2010 to Nov 2011 | CPB, MR, LBR, PR, Preterm, LBW |
| Shapiro 2011a [16] | All were first-time IVF patients with cycle day 3 FSH <10 mIU/mL and 8–15 antral follicles. | 24–41 years | RCT | No statement | IR, CPR, MR, MPR, OPR, PR |
| Shapiro 2011b [23] | Patient must be undergoing her first IVF cycle; cycle day 3 FSH <10 IU/L; and >15 antral follicles | No statement | RCT | No statement | IR, CPR, MR, MPR, OPR, PR |
| Shapiro 2013 [49] | Single-blastocyst transfer. | 33.8±4.7/33.8±4.7 | Matched cohort study | Dec 2003 to Dec 2011 | CPR, MR, MPR, OPR, PR |
| Shavit 2017 [6] | Singletons born after fresh or vitrified-warmed single BT | Any age | Retrospective cohort study | Dec 2008 to Dec 2012 | Preterm, GDM, PIH, LGA, SGA, LBW, HBW, Neonatal malformations |
| Shih 2008 [17] | Neonatal perinatal statistics unit Australia | Any age | Matched cohort study | 1978 to 2005 | Preterm, LBW, Neonatal malformations |
| Vuong 2016 [50] | Non-PCOS infertile couples undergoing IVF/ICSI | No statement | RCT | No statement | MPR, LBR, MPR, OPR, EPR |
| Vuong 2018 [51] | Non-PCOS infertile women who were undergoing a first or second IVF cycle 3 | 32±4 /32±4 | RCT | No statement | IR, CPR, MR, MPR, LB, OPR, EPR, OHSS |
| Authors | Study Title | Description | Participants | Study Design | Start Date | Outcomes |
|---------|-------------|-------------|--------------|--------------|-------------|----------|
| Walls 2014 [52] | Women with PCOS | Any age | 122/179 | Retrospective case–control study | Mar 2007 to Dec 2012 | CPR, MR, LBR, PR |
| Wang 2005 [53] | Infants conceived through ART procedures and born in Australia | Any age | 7676/3824 (singleton) | Retrospective cohort study | 1996 to 2000 | LBW. |
| Wei 2019 [7] | Women with regular menstrual cycles undergoing their first cycle of in-vitro fertilization | 28.8 (3.0) / 28.8 (3.0) | 825/825 | RCT | Aug 2016, to Jun 2017 | IR, CPR, MR, MPR, LBR, OPR, PR, EPR, OHSS, PP, PH, Preterm, GDM, PIH, LGA, SGA, Neonatal malformations |
| Wennerholm 1997 [54] | Birth after IVF with cryopreserved–thawed embryos in Sweden | 34.0±3.1/33.6±3.3 | 209/209 (160/160 singletons) | Matched cohort study | Jun 1990 to Jul 1995 | PH, Preterm, GDM, PIH, LBW |
| Wennerholm 2013 [55] | Singleton conceived after FET in Denmark, Norway and Sweden | 33.3±4.0/33.7±3.9 | 42242/6647 (singleton) | Retrospective cohort study | Until Dec 2007 | Preterm, LGA, SGA, VSGA, LBW, HBW, Perinatal mortality |
| Wikland 2010 [56] | Children born after vitrified BT or fresh BT | 34.7 (22.0–44.0)/35.4 (26.3–45.3) | 203/103 (singleton) | Retrospective cohort study | Jan 2006 to May 2008 | MR, LBR, PR, EPR, PP, PA, GDM, PIH, LGA, SGA, LBW |
| Wu 2014 [57] | High responder patients diagnosed as primary infertility with more than 15 oocytes retrieved | 29.02±2.87/29.05±2.48 | 50/69 | Retrospective cohort study | Jan to Nov 2012 | IR, CPR, MPR, |
| Yang 2015 [58] | Patients with elevated progesterone level (P> 6 nmol/L) on the HCG day in IVF/ICSI cycle | Between 20 and 40 years | 43/42 | Retrospective cohort study | Mar 2011 to Mar 2012 | IR, CPR, LBR, PR |
| Zhang 2018 [59] | Women with PCOS | 28.1±3.1/28.4±2.9 | 212/250 (singleton) | Retrospective cohort study | Jun 2013 to Jul 2015 | GDM, pre-eclampsia, Preterm, LGA, SGA |

**Figures**
Figure 1

Forest plot of comparison for (A) implantation rate and (B) pregnancy rate.
Figure 2

Forest plot of comparison for (A) ongoing pregnancy rate and (B) ectopic pregnancy rate.
Figure 3

Forest plot of comparison for (A) hypertension and pre-eclampsia, (B) OHSS.
Figure 4

Forest plot of comparison for (A) placental abruption and (B) preterm<37W.
Figure 5

Forest plot of comparison for (A) large for gestational age, (B) small for gestational age, (C) high birth weight>4000g and (D) low birth weight<2500g.
Figure 6

Forest plot of comparison for (A) congenital anomaly and chromosomal aberrations, (B) circulatory system diseases, (C) respiratory system diseases and (D) nervous system diseases.

Supplementary Files

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