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The impact of assisted reproductive technology treatments on maternal and offspring outcomes in singleton pregnancies: A review of systematic reviews

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Abstract:

Objectives: Assisted reproductive technology (ART) treatments are commonly used to aid conception in subfertile couples. We aimed to evaluate the risks of adverse maternal and offspring outcomes in singleton pregnancy conceived with different ART treatments and techniques.

Evidence review: We searched MEDLINE, EMBASE, CENTRAL and HTA until December 2020 for all systematic reviews evaluating adverse outcomes in pregnancies conceived with various ART techniques, autologous or donor gametes, and embryo development stages. We assessed review quality using the AMSTAR2 tool risk (RR) or odds ratio (OR) with 95% confidence intervals (CI) from the top quality reviews for each of the outcomes of interest across the identified ART treatments and population subgroups.

Results: We included 24 systematic reviews, most reported on observational studies. Compared to spontaneous conception, ART pregnancies had a higher risk of placenta previa (PP) (RR 3.71, 95%CI 2.67-5.16), antepartum haemorrhage (APH) (RR 2.11, 95%CI 1.86-2.38), preterm birth (PTB) (RR 1.71, 95%CI 1.59-1.83), very preterm birth (VPTB) (RR 2.12, 95%CI 1.73-2.59), small for gestational age (SGA) (RR 1.35, 95%CI 1.20-1.52), low birthweight (LBW) (RR 1.61, 95%CI 1.49-1.75) and very low birthweight (VLBW) (RR 2.12, 95%CI 1.84-2.43).

Frozen vs fresh embryo transfer was associated with a lower risk for PTB (RR 0.90, 95%CI 0.84-0.97), SGA (RR 0.61, 95%CI 0.56-0.67), LBW (RR 0.72, 95%CI 0.67-0.77) and VLBW (RR 0.76, 95%CI 0.69–0.82). Embryo transfer at blastocyst vs cleavage showed higher risk for PTB (RR 1.10, 95%CI 1.01-1.20) and large for gestational age (LGA) (RR 1.12, 95%CI 1.03-1.21) with lower risk for SGA (RR 0.84, 95%CI 0.76-0.92).

Using donor vs autologous oocytes increased the odds of PTB (OR 1.57, 95%CI 1.33-1.86), LBW (OR 1.94, 95%CI 1.10-3.41) and VLBW (OR 1.37, 95%CI 1.22–1.54) as well as maternal complications (postpartum haemorrhage OR 1.96, 95% CI 1.20-3.20, gestational diabetes OR 1.27 95%CI 1.03-1.56, hypertensive disorders of pregnancy OR 2.63, 95%CI 2.17-3.18, and caesarean section OR 2.28, 95%CI 2.14-2.42).

Conclusions: ART treatments are associated with increased risks of adverse maternal and offspring outcomes, especially with donor oocytes. The characteristics of ART treatment should be incorporated into prenatal care planning to mitigate those risks.

PROSPERO registration: CRD42020182612, registered 03/09/2020.

keywords: in-vitro fertilisation, pregnancy, maternity, assisted conception, antenatal, intrapartum, offspring, systematic review.

Highlights:

-Assisted reproductive technology (ART) treatments are common, however, their impact on maternal and offspring outcomes remains uncertain.

-Compared to spontaneous conception, ART pregnancies had higher risk of placental abnormalities, fetal growth abnormalities, hypertensive disorders of pregnancy, gestational diabetes, caesarean section.

-Frozen vs fresh embryo transfer was associated with a lower risk for preterm birth and fetal growth abnormalities.

-Embryo transfer at blastocyst vs cleavage showed higher risk for preterm birth and fetal growth abnormalities.

-Donor vs autologous oocytes increased the odds of preterm birth and other maternal complications (postpartum haemorrhage, gestational diabetes, hypertensive disorders of pregnancy).

-Our findings highlight the increased risk of adverse maternal and offspring outcomes in ART pregnancies which varied per the ART treatments and techniques used.

-There is a need to incorporate the characteristics of ART treatments at the time of pregnancy booking to mitigate ensuing risks in the antenatal and intrapartum period.

Introduction:

The past few decades saw the widespread adoption of assisted reproductive technology (ART) as a mainstream treatment for subfertility, offering hope to thousands of affected couples worldwide(1,2). To date, over 8 million children were born with ART treatments and more than 2.5 million cycles are performed yearly(3).

Several interventions were introduced to improve the safety and effectiveness of ART treatments in the pre-conception period such as single best embryo transfer(4) and elective embryo freezing in women at risk of ovarian hyperstimulation(5). However, most of the morbidity associated with ART treatments manifest during pregnancy and labour, increasing the risk of several adverse maternal and offspring outcomes(6–9). Some of these risks, such as abnormal placentation, could be directly linked to the process of ART (10), while others are attributed to inherent demographic or medical factors in women undergoing ART such as advanced maternal age and obesity which increase the risk of perinatal mortality in this cohort(11). Often, these risks go unrecognised leading to suboptimal antenatal and intrapartum care for women with ART pregnancies(12,13). Highlighting the increased risk status in this cohort is particularly relevant as care for subfertile women is often segregated among fertility and maternity teams leading to fragmented care and inadequate antenatal risk assessment screening process. Several systematic reviews and meta-analyses aimed to evaluate the maternal and offspring risk associated with different ART treatments within different subfertile population groups (9,10,14). However, the permeation of this evidence to inform clinical practice and evidence-based guidelines remains heterogeneous. Comprehensive evidence synthesis is therefore needed to evaluate these outcomes across all ART treatments and identify optimal interventions and screening pathways to mitigate

those risks in the antenatal and intrapartum period. We aimed to address this research need by conducting a comprehensive review of systematic reviews to evaluate the risks of adverse perinatal outcomes (up to 28 days post-delivery) in women with singleton pregnancy following ART treatments.

Methods:

We conducted our review using a prospectively registered protocol (CRD42020182612) and reported in line with established guidelines(15).

Search strategy

We searched electronic databases (MEDLINE, EMBASE, Cochrane CENTRAL and HTA) from inception to December 2020 for all systematic reviews that met our inclusion criteria. We used several MeSH terms and keywords (Appendix 1) and combined them using the Boolean operators AND/OR to screen for relevant citations. No search filters or language restrictions were applied. We performed complementary searches in Google Scholar and Scopus to identify any missed citations and also manually searched the bibliographies of potentially relevant articles.

Review selection and inclusion

Two authors (AS and JM) independently screened the titles and abstracts to identify relevant citations. Then, we screened full-text articles against our inclusion criteria.

Discrepancies were resolved through consultation with the senior author (BHA). We included all systematic reviews that reported on maternal or offspring outcomes of interest in women with a singleton pregnancy following any ART treatment. Reviews that reported partially on the selected outcomes were included. We excluded reviews that reported exclusively on pregnancies conceived following ovulation stimulation, intrauterine insemination, gamete intrafallopian transfer and those reporting exclusively on multiple pregnancies, immediate outcomes of conception, first-trimester pregnancy outcomes following ART, and longterm neonatal outcomes (beyond 28 days of age). Non-systematic and narrative reviews were excluded, as well as those reporting on animal or laboratory findings.

Quality assessment

We aimed to systematically evaluate and identify the best quality systematic review to summarise evidence on each of the outcomes of interest identified across the different ART treatments and subgroups. Therefore, we assessed the quality of included reviews in duplicate (AS and JM) using the AMSTAR2 tool(16). Reviews were assessed for their methodological quality in the following domains: if they were prospectively registered with a defined PICO question, conducted a comprehensive literature search; described the study selection and inclusion criteria sufficiently; reported and investigated sources of bias; reported and adjusted for heterogeneity and sources of bias in included studies, and if they used an adequate meta-analysis methodology. We generated an overall confidence rating based on the weaknesses of each review and categorised them into high, moderate, low or critically low quality.

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143

144 *Outcomes*

145 We reported on the following adverse maternal and offspring outcomes selected a priori in
146 line with the core outcome set for fertility treatments (17): abnormal placentation
147 (antepartum haemorrhage, abnormally invasive placenta, placenta previa, placental
148 abruption), prematurity (preterm labour, very preterm labour, admission to the offspring
149 unit), birth weight (small for gestational age, low birth weight, large for gestational age),
150 maternal morbidity in pregnancy (postpartum haemorrhage, gestational diabetes, pre-
151 eclampsia, pregnancy-induced hypertension, maternal admission to HDU, caesarean
152 section), perinatal mortality (stillbirth and offspring death), and fetal congenital anomalies.
153 Definitions of reported outcomes are detailed in Appendix 2.

154

155 *Data extraction and evidence synthesis*

156 We extracted data in duplicate (AS and JM) using a piloted electronic collection tool on the
157 following characteristics: the review publication year and journal, inclusion-exclusion
158 criteria, type and number of included primary studies, characteristics of included
159 population, characteristics of evaluated ART interventions, all relevant maternal and
160 offspring outcomes, prospective registration, and the overall risk of bias and quality of
161 included primary studies in each review.

162 We mapped out the evidence across included reviews and summarised effect estimates for
163 each of the pre-selected outcomes using the most up to date review, with the largest

sample size and best quality as per AMSTAR2 tool. We reported on dichotomous outcomes using risk ratio (RR), odds ratio (OR) or Peto odds ratio (pOR) and for continuous outcomes using weighted mean difference (WMD), mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CI). Where possible we reported each outcome first in ART vs spontaneous conception pregnancies then reported on the effect estimates within available subgroups based on oocyte source and embryo development stage. The reviews' characteristics were described using percentages and natural frequencies.

Results:

Characteristics of included reviews

Our search identified 1967 citations, of these we reviewed 108 articles in full against our inclusion criteria and included 24 systematic reviews (*Figure 1*). Most reviews included observational studies (23 reviews included cohort studies; 8 included case-control studies; 5 included RCTs). A third of the included reviews compared maternal and offspring outcomes between assisted and spontaneously conceived pregnancies (8 reviews, 268 primary studies and 16,352,609 women). Eight reviews compared outcomes between different embryo development stages and subgroups (5 blastocyst vs cleavage, 3 frozen vs fresh) and only two reviews specifically compared pregnancy outcomes in donor vs autologous oocytes (Table 1). Most reviews were conducted in Europe (6 UK, 2 Greece, 1 Spain, 1 Italy, 1 Denmark). Five were from Asia (4 China, 1 India) and five were from North America (4 Canada, 1 USA).

Quality of included reviews

The overall quality of included reviews was moderate with most reviews scoring high for having a defined PICO question, justifying their inclusion criteria, using duplicate study selection and data extraction process, and using appropriate statistical analysis methods (Figure 2). Six reviews were registered prospectively (6/24, 25%) and twelve provided a justification for excluded studies (12/24, 50%). Only three reviews fully assessed the risk of bias in included studies and accounted for it when interpreting results (3/24, 13%) while two thirds (16/24, 67%) explained detected heterogeneity. Only five reviews were judged to be of high quality (5/24, 21%) with high confidence in the review results, while 14 (14/24, 58%) were of moderate quality and five (5/24, 21%) reviews were of low quality (*Figure 2, Appendix 3).*

ART vs spontaneous conception

Overall, ART pregnancies were associated with a higher risk for maternal and offspring adverse outcomes (Table 2). The risk of abnormal placentation (placenta previa RR 3.71, 95%CI 2.67-5.16; placental abruption RR 1.83, 95%CI 1.49-2.24) and the risk of antepartum haemorrhage (RR 2.11, 95%CI 1.86-2.38) were higher in ART pregnancies. There was also a significant risk of preterm (RR 1.71, 95%CI 1.59-1.83) and very preterm birth (RR 2.12, 95%CI 1.73-2.59) compared to spontaneous conception (Figure 3).

Babies conceived with ART were more likely to be small for gestational age (RR 1.35, 95%CI 1.20-1.52), have low birth weight (RR 1.61, 95%CI 1.49-1.75), and very low birth weight (RR

2.12, 95%CI 1.84-2.43). There was also a higher risk of perinatal mortality (RR 1.57, 95%CI 1.46-1.70) and admission to the neonatal unit (RR 1.58, 95%CI 1.42-1.77), although neonatal death was not different between both groups (RR 1.30, 95% CI 0.08-21.33) (Figure 3). There was also a higher risk of congenital abnormalities RR 1.48 (95% CI 1.29-1.70) (Table 2).

Mothers conceiving with ART were at higher risk of hypertensive disorders of pregnancy (RR 1.49, 95%CI 1.39-1.59) including pre-eclampsia (RR 1.29, 95%CI 1.06-1.57) and pregnancy-induced hypertension (RR 1.30, 95%CI 1.04-1.62). Additional maternal risks with ART pregnancies included gestational diabetes mellitus (RR 1.53, 95%CI 1.39-1.69), caesarean section (RR 1.58, 1.48-1.70) and postpartum haemorrhage (RR 1.29, 95%CI 1.06-1.57) (Figure 3). Evidence on the risks associated with single embryo transfer compared to spontaneous conception was of limited quality and low confidence (Table 2).

Embryo development subgroups

There was a lower risk of preterm birth with frozen versus fresh embryo transfer (RR 0.90, 95%CI 0.84-0.97). Embryo transfer at blastocyst stage or with fresh blastocyst stage was associated with a higher risk of preterm birth compared to cleavage stage transfer (RR 1.10, 95%CI 1.01-1.20 and RR 1.15, 95%CI 1.05-1.25 respectively). There was no difference when comparing frozen blastocyst with cleavage stage transfer (RR 1.11, 95%CI 0.99-1.25) (Table 3).

The use of frozen embryos was associated with a lower risk for small for gestational age (RR 0.61, 95%CI 0.56-0.67), low birth weight (RR 0.72, 95%CI 0.67-0.77) and very low birth

weight RR 0.76 (95%CI 0.69–0.82) in addition to a higher risk for large for gestational age (RR 1.54, 95%CI 1.48-1.61). Blastocyst embryo transfer compared to transfer at cleavage stage was associated with lower risk for small for gestational age (RR 0.84, 95%CI 0.76-0.92), higher risk for large for gestational age (RR 1.12, 95%CI 1.03-1.21), but did not affect perinatal mortality (RR 1.48, 95%CI 1.09-2.02). There was limited evidence to assess these outcomes within fresh vs frozen subgroups (Table 2 and Table 3).

Maternal outcomes were similar across the different embryo development subgroups though there was evidence of a higher risk of hypertensive disorders of pregnancy with frozen versus fresh embryo transfer (RR 1.29, 95%CI 1.07-1.56).

Oocytes

The use of donor vs autologous oocytes in ART pregnancies increased the odds of preterm birth (OR 1.57, 95% CI 1.33-1.86) and very preterm birth (OR 1.80, 95% CI 1.51-2.15) (Table 4). Low birth weight (OR 1.94, 95%CI 1.10-3.41) and very low birth weight (OR 1.37, 95%CI 1.22–1.54) were more common with donor oocytes (Table 4). This is in contrast to the odds for small for gestational age which were lower in ART pregnancies with donor compared to autologous oocytes (OR 0.83, 95%CI 0.78-0.89) and no difference in the odds of large for gestation age (OR 0.89, 95%CI 0.57-1.40).

Maternal pregnancy complications were also higher with donor compared to autologous oocytes, including odds of postpartum haemorrhage (OR 1.96, 95% CI 1.20-3.20), gestational diabetes (OR 1.27 95% CI 1.03-1.56), hypertensive disorders of pregnancy (OR 2.63, 95% CI 2.17-3.18), preeclampsia (OR 2.64, 95% CI 2.29-3.04), pregnancy-induced

hypertension (OR 2.16, 95% CI 1.79-2.62); and caesarean section (OR 2.28, 95% CI 2.14-2.42). Those risks were overall consistent for both fresh and frozen embryo transfer with donor oocytes, although the evidence on the different subgroups was limited to a small number of observational studies (Table 4).

Discussion:

Summary of main findings

Our findings show an overall increase in the risk of adverse maternal and offspring outcomes associated with pregnancies of assisted conception compared to spontaneous conception. These risks were prevalent across the different ART treatments used which suggest a higher association with adverse pregnancy outcomes in this cohort. This is particularly relevant as most antenatal guidelines propose standardised risk screening pathways to identify women at risk of adverse pregnancy outcomes(18–30), but, ART pregnancies are not uniformly identified as a high-risk group in available guidelines(31).

The risk of placental pathology, including placental previa, abruption and haemorrhage, was particularly high with ART treatments which highlight the importance of early screening and assessment to mitigate the risk of serious maternal morbidity in this cohort. Similarly, ART treatments increased the risk of preterm birth and suboptimal fetal growth especially with donor oocyte conception, which could emphasise the value of routine serial ultrasound fetal measurement and cervical length screening in these pregnancies.

The risk of adverse maternal and offspring outcomes varied across the evaluated subgroups per type of ART treatment and source of gametes used. Incorporating these risks into the antenatal and intrapartum care plan could therefore help to generate a more individualised risk assessment and optimise patients' counselling. Still, available evidence was of poor quality to enable accurate assessment of several important outcomes (e.g stillbirth) across all relevant subgroups (e.g. donor oocyte).

Strength and limitations

We employed a comprehensive methodology to identify the best quality evidence and generate risk estimates on pre-selected outcomes of interest. We registered our review prospectively and evaluated the quality of included reviews using the AMSTAR2 tool(16). We elected to use the most up to date, most comprehensive and top quality reviews as per AMSTAR2 to offer balanced evidence synthesis and reduce the risk of bias across included reviews.

The evidence summarised here is largely observational depicting an association between different ART treatments and adverse pregnancy outcomes. Establishing causality requires comparative research which is outside the scope of our review. Our findings have several limitations. Firstly, we were unable to report on all relevant outcomes (e.g. stillbirth) due to the variation and the quality of outcomes reporting. Additionally, the definitions of several outcomes may have varied across included reviews and their primary studies. This increased the uncertainty in reported effect estimates, especially within small subgroups. For

example, we detected conflicting evidence of higher risk for low birth weight and a lower risk for small for gestation age with the use of donor vs autologous oocytes. Confidence in this evidence is low especially given the reported statistical heterogeneity (I^2>70)(14). Majority of the included reviews reported using pooled risk or odds ratio highlighting statistical significance for included outcomes. It is important, however, to consider the absolute risk and event rate, particularly for rare outcomes to accurately evaluate their clinical significance.

Clearly, several effect modifiers could impact the risk of adverse outcomes in couples seeking ART such as BMI, cause of subfertility, smoking status and other comorbidities. This is particularly relevant when comparing certain subgroups such as the effect of maternal age in the autologous vs donor oocytes groups. Other outcomes such as preterm birth and low birth weight could be iatrogenic and driven by other complications (e.g. pre-eclampsia). We were unable to adjust for these factors across included reviews which could only be accounted for in an individual patient data meta-analysis. Similarly, we were unable to assess the risk of publication bias often featured in observational studies. To reduce the risk of compounding bias, we used the AMSTAR tool to objectively evaluate and select the best quality reviews that accounted for such effect modifiers and other sources of bias in their primary analysis. Therefore, we argue that our review summarised the best quality evidence pending future efforts to produce a detailed individual patient data meta-analysis using primary data.

Lastly, our selected outcomes were focused to evaluate short term maternal and offspring morbidity in ART pregnancies. Several important medium and longer-term outcomes (e.g. offspring neurodevelopment) are seldom reported in follow up cohorts of ART

pregnancies(32). Incorporating these outcomes in future evidence synthesis is important to better evaluate the overall risks associated with ART treatments.

Implications for clinical practice

Our findings suggest the need for effective implementation of modified prenatal care pathways that highlight ART treatments as a contributing risk factor for adverse maternal and offspring outcomes. While some antenatal guidelines identify the added risk with ART treatments(33), a comprehensive risk assessment process is needed at booking for the pregnancy taking into account the different ART treatments used.

Several simple interventions could be adopted in practice to screen for the prenatal risks in women with ART pregnancies. However, studies are required to evaluate the cost-effectiveness of such interventions and aid their implementation into different care settings in collaboration with all relevant stakeholders(34).

Effective collaboration among fertility and obstetric healthcare professionals is needed to raise awareness on the health needs of women with ART pregnancies and to enable continuity care from the pre-conception to the post-partum period(35–37). This is particularly relevant in countries where ART treatments are offered in small private fertility units with no direct links to maternity care hospitals(38). As such, comprehensive multi-disciplinary care pathways are needed to address this health need and optimise the care of women with ART pregnancies.

Future research need

ART is evolving rapidly with novel techniques introduced regularly to improve the chances of conception and pregnancy rates. However, there remains less focus on improving maternal and child health once ART treatments are concluded. Longterm follow up studies are still needed to evaluate the safety and effectiveness of these treatments and to better counsel couples in the pre-conception period. As more women with multi-morbidity rely on ART treatments to start their families, there is a need for specialised antenatal and intrapartum care services to mitigate ensuing risks in this high risk group(39).

Currently, several screening pathways are adopted uniformly in antenatal care guidelines to detect early disease in high-risk pregnancies such as serial fetal growth scanning and regular blood pressure measurement(31). There is a need to evaluate the suitability and effectiveness of these interventions in women with ART pregnancies and whether any additional screening measures are needed. For example, early scanning for cervical length assessment and placental localisation could be helpful to better plan the antenatal care of women at risk of preterm birth and placenta praevia within tertiary specialised settings(40–42). Similarly, certain biomarkers could facilitate early detection of fetal growth abnormalities particularly in higher-risk subgroups such as pregnant women with donor oocytes(43). Prospective studies are needed to evaluate the cost-effectiveness of such measures in clinical practice.

Poor outcomes reporting limited our ability to synthesise precise evidence on maternal and offspring risk in this cohort. While a standardised core outcome set currently exists for studies on fertility treatment(44), its uptake and impact on evidence synthesis remain

unclear. We encourage future researchers to adopt the suggested minimal standardised reporting on core outcomes to aid future evidence synthesis and provide clarity to counsel couples undertaking ART treatments. Similarly, most of the included reviews and their primary studies focused on singleton pregnancies without considering these outcomes in multiple pregnancies. Giving that ART remains a major cause for twin pregnancy, evaluating these outcomes in such subgroups is of great importance to inform future clinical practice.

Conclusion: ART treatments are associated with increased risks of adverse maternal and offspring outcomes, especially with donor oocytes. The characteristics of ART treatment should be incorporated into prenatal care planning to mitigate those risks.

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Data availability: Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors contribution: JM, AS, and NB ran the search, extracted data and conducted the initial analysis. SQ, SDK, EY, and AD contributed equally to the data interpretation and the final manuscript. BHA conceived the idea, wrote the protocol and the final manuscript and supervised the study conduct.

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529 **Figure legends**

530 **Figure (1)**: Selection and inclusion process for systematic reviews evaluating maternal and
531 offspring outcomes in singleton pregnancies following assisted reproductive technology.

532

533 **Figure (2):** Quality assessment for systematic reviews systematic reviews evaluating the risk
534 of adverse maternal and offspring outcomes associated with singleton pregnancies
535 following assisted reproductive technology using the AMSTAR2.

536

537 **Figure (3):** Forest plot of adverse maternal and offspring outcomes in singleton pregnancies
538 following assisted reproductive technology compared to spontaneous conception.

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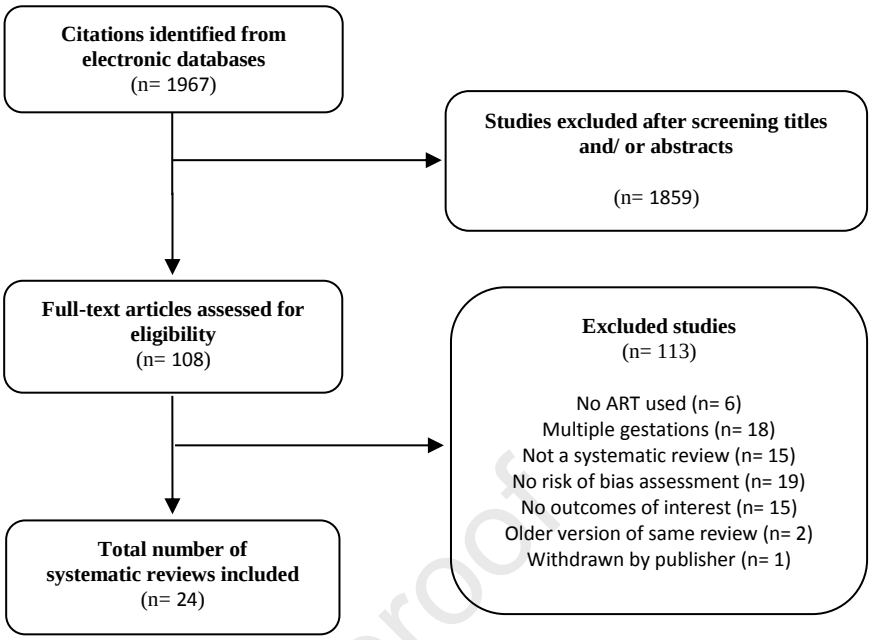

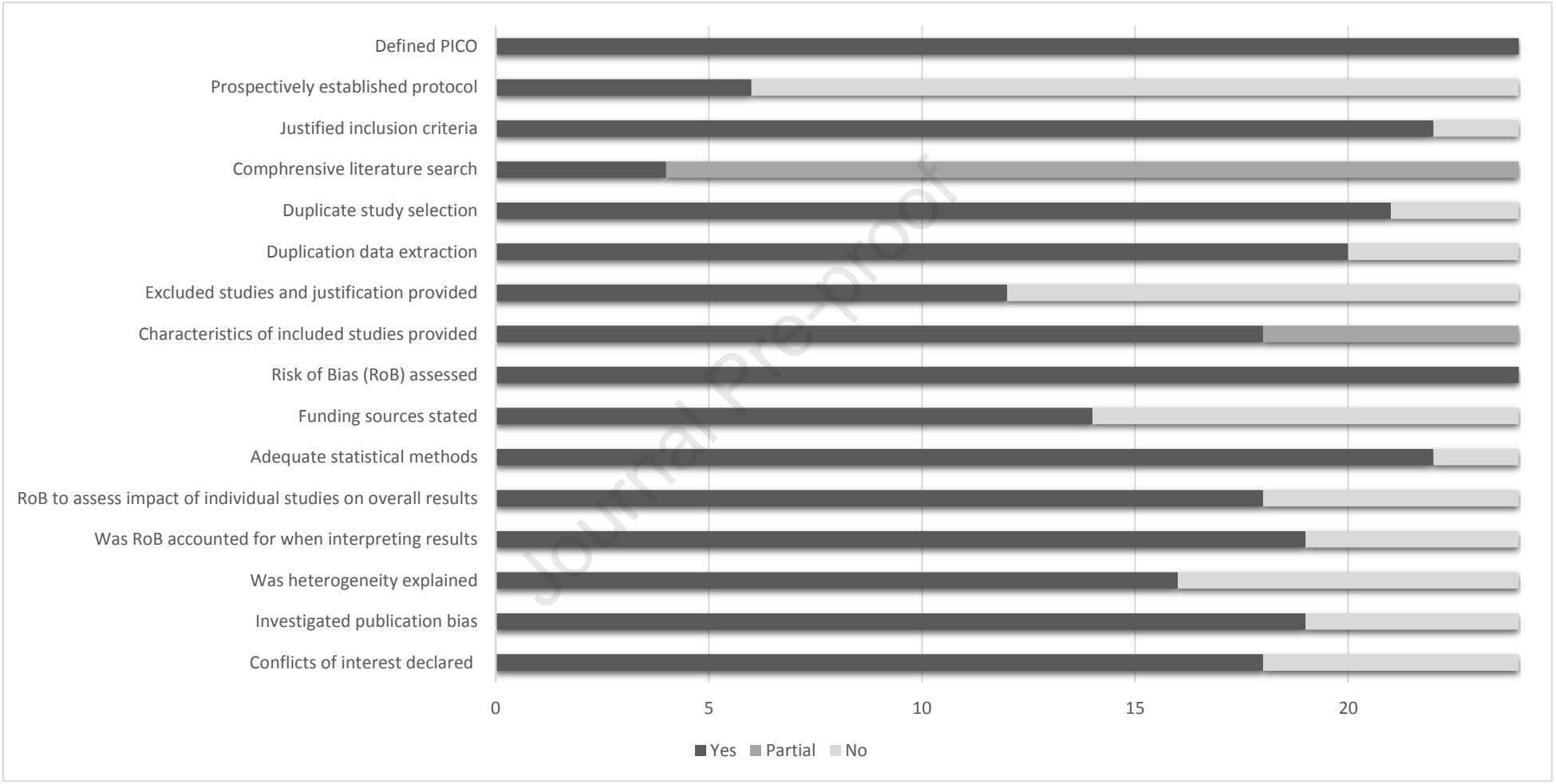

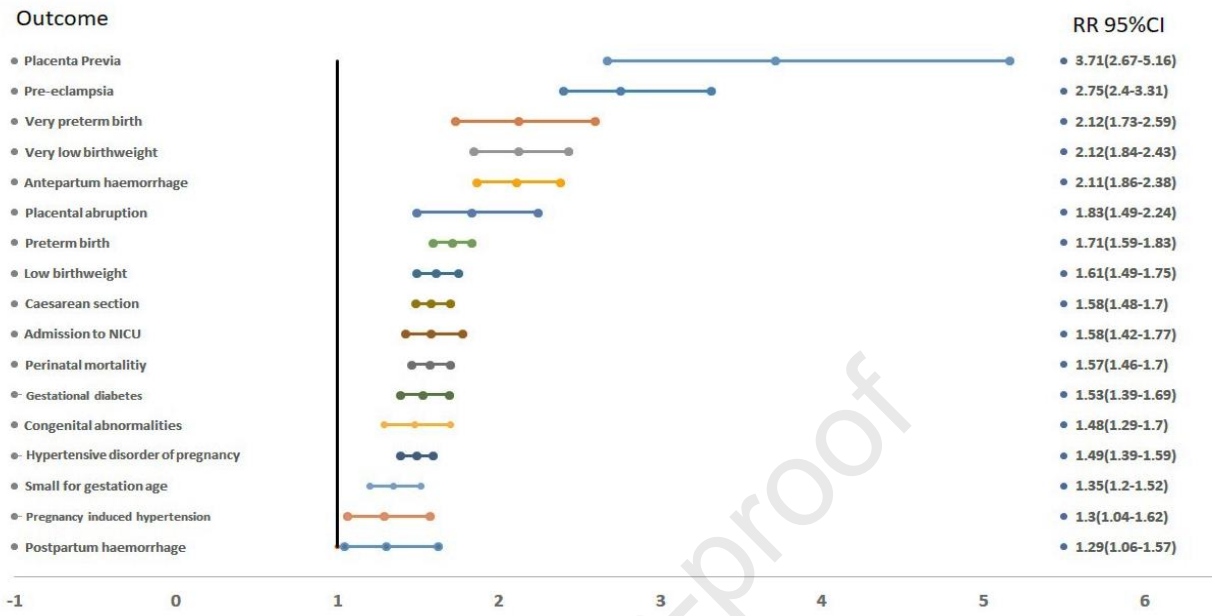

*NICU: Neonatal intensive care unit.

**Pre-eclampsia estimates converted from OR to RR for visualisation purposes.

Table (1): Characteristics of included systematic reviews evaluating the risk of adverse maternal and offspring outcomes associated with singleton pregnancies following assisted reproductive technology compared to spontaneous conception**.**

Author (year)	Country	Included study types	ART group	Comparison group	Total number of studies*	Total number intervention group **	Outcomes included in this review	ROB or quality tool used	Review quality (AMSTAR2)
Adams (2017)	Australia	Cohort studies	Donor sperm IVF	Non-donor sperm (IVF or spontaneous conception)	8	> 424238	Congenital abnormalities	Modified Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument	Moderate
Alviggi (2018)	Italy	Cohort studies	Blastocyst stage transfer (Fresh and frozen)	Cleavage stage transfer (Fresh and frozen)	14	339500	Preterm birth, very preterm birth, small for gestational age, low birth weight, very low birth weight, large for gestational age, perinatal mortality	(a) Newcastle-Ottawa scale (b) GRADE	Moderate
Armstrong (2019)	United Kingdom	RCTs	Time lapse series with conventional morphological assessment using still TLS images	Conventional incubation and assessment	14	90231	Stillbirth	(a) Cochrane risk of bias tool (b) GRADE	High
Bosdou (2020)	Greece	Cross-sectional, matched and unmatched	IVF/ICSI	Spontaneous conception	38	1934494	Gestational diabetes	Newcastle-Ottawa Scale	High
Chen (2018)	China	Cohort studies	IVF / ICSI	Spontaneous conception	34	6864336	Congenital anomalies	Newcastle-Ottawa Scale	Moderate
Dar (2014)	Canada	Cohort studies	Blastocyst stage transfer	Cleavage stage transfer	6	77195	Preterm birth , very preterm birth, low birth weight, very low birth weight, congenital abnormalities	Newcastle-Ottawa Scale	Moderate
Grady (2012)	Canada	Cohort studies, case-control	IVF (single embryo transfer)	Spontaneous conception	16	2109	Placenta previa, placental abruption, preterm birth, , very preterm birth, admission to neonatal unit, small for gestational age, low birth weight, very low birth weight. gestational diabetes, preeclampsia, neonatal death	(a) Newcastle-Ottawa scale (b) Cochrane handbook for RCTs	Low
Hansen (2013)	Australia	Cohort studies	(a) IVF (b) ICSI	Spontaneous conception	45	91879	Congenital anomalies	CASP	Low
Jeve (2016)	United Kingdom	Cohort studies, case-control	Oocyte donation IVF	IVF with autologous oocyte	11	81752	Pre-eclampsia, pregnancy induced hypertension	(a) Newcastle-Ottowa scale (b) Cochrane risk of	Moderate

							bias tool	
Kamath (2017)	India	RCT, cohort studies	Stimulated IVF	Natural cycle or modified natural cycle IVF	34	97698	Preterm birth, very preterm birth, small for gestational age, large for gestational age, low birth weight, very low birth weight, large for gestational age, congenital abnormalities	(a) CASP (b) Cochrane risk of bias tool	Low
Maheshwari (2013)	United Kingdom	Cohort studies	Blastocyst stage transfer	Cleavage stage transfer	8	> 687082	Placenta previa, placental abruption, preterm birth, , very preterm birth, small for gestational age, low birth weight, very low birth weight, preeclampsia, perinatal mortality, congenital abnormality	CASP	Moderate
Maheshwari (2018)	United Kingdom	RCT, cohort studies	Frozen embryo IVF	Fresh embryo IVF	26	not reported	Antepartum haemorrhage, preterm birth, very preterm birth, small for gestational age, low birth weight, very low birth weight, admission to neonatal unit, large for gestational age, hypertensive disorders of pregnancy, , perinatal mortality, congenital abnormalities	CASP	High
Martins (2016)	Brazil	Cohort studies	Blastocyst stage transfer	Cleavage stage transfer	12	195325	Placenta previa, abnormal placentation, placenta abruption, antepartum haemorrhage, preterm birth, , very preterm birth, small for gestational age, low birth weight, very low birth weight, large for gestational age, postpartum haemorrhage gestational diabetes, hypertensive disorders of pregnancy, , Caesarean section, perinatal mortality, stillbirth, congenital abnormalities	(a) Newcastle-Ottawa Scale (b) GRADE	High
Mascarenhas (2017)	United Kingdom	Cohort studies	Oocyte donation IVF (Fresh and frozen)	Autologous oocyte IVF (Fresh and frozen)	7	97700	Preterm birth, very preterm birth, low birth weight, very low birth weight	CASP	Low
Masoudian (2016)	Canada	Cohort studies, case-control	Oocyte donation IVF/ICSI	IVF/ICSI/spontaneous conception	19	86515	Preeclampsia, pregnancy induced hypertension	MINORS criteria (Methodological Index for Non-Randomized Studies)	Moderate
Moreno-Sepulveda	Spain	Cohort studies, case-control	Oocyte donation IVF (Fresh and	Autologous oocyte IVF (Fresh and	23	410628	Placenta previa, placental abruption, preterm birth, very preterm birth,	(a) Newcastle-Ottawa Scale	Moderate

(2019)			frozen)	frozen)			small for gestational age, low birth weight, very low birth weight, large for gestational age, postpartum haemorrhage gestational diabetes, hypertensive disorders of pregnancy, preeclamsia, pregnancy induced hypertension, caesarean section	(b) GRADE	
Pandey (2012)	United Kingdom	Cohort studies	(a) IVF/ICSI (b) Frozen embryo transfer (c) Single embryo transfer	Spontaneous conception	30	not stated	Preterm birth, very preterm birth, admission to neonatal unit, small for gestational age, low birth weight, very low birth weight, gestational diabetes, hypertensive disorders of pregnancy, pregnancy induced hypertension, caesarean section, perinatal mortality, congenital abnormalities	CASP	High
Qin (2016)	China	Cohort studies	IVF/ICSI	Spontaneous conception	50	2441611	Placenta previa, placental abruption, antepartum haemorrhage, preterm birth, very preterm birth, small for gestational age, low birth weight, very low birth weight, postpartum haemorrhage, gestational diabetes, pregnancy induced hypertension, caesarean section, perinatal mortality, congenital abnormalities	Modified Newcastle-Ottawa Scale	Moderate
Sha (2018)	China	RCT, cohort studies	Frozen embryo transfer	Fresh embryo transfer	31	257922	Preterm birth, low birth weight	Newcastle-Ottawa Scale	Moderate
Storgaard (2016)	Denmark	Cohort studies	Oocyte donation	(a) IVF/ ICSI (b) Spontaneous conception	35	> 1134000	Preterm birth, small for gestational age, low birth weight, postpartum haemorrhage gestational diabetes hypertensive disorders of pregnancy, pre-eclampsia caesarean section	(a) Swedish Agency for Health Technology Assessment and Assessment of Social Services (b) GRADE	Moderate
Thomopoulos (2016)	Greece	Cohort studies	(a) Oocyte donation (b) ICSI (c) IVF (d) IVF/ICSI	Spontaneous conception	66	7038029	Hypertensive disorders of pregnancy, preeclampsia, h	Novel assessment tool	Moderate
Vermey	Australia	Cohort studies	Frozen embryo	Non-ART	33	6178944	Placenta previa, placental abruption	(a) Modified	Moderate

(2018)			transfer					Newcastle-Ottawa Scale (b) GRADEPRO	
Wang (2017)	China	Cohort studies	Blastocyst stage transfer	Cleavage stage transfer	12	450155	Preterm birth, very preterm birth, small for gestational age, low birth weight, very low birth weight, large for gestational age	Newcastle-Ottawa Scale	Moderate
Zhao (2016)	China	Cohort studies	IVF/ICSI	Frozen embryo transfer	13	126911	Stillbirth	Newcastle-Ottawa Scale	Low

*Total number of studies included in the systematic review regardless of eligibility, number of studies may vary per outcome
** Total number of women included in the systematic review regardless of eligibility, number of women may vary per outcome

Table (2): Risk of adverse maternal and offspring outcomes associated with singleton pregnancies following assisted reproductive technology compared to spontaneous conception**.**

Outcome	Comparison	Systematic review	Primary studies (participants)	Risk/Odds ratio (95% confidence intervals)
Placenta previa	ART vs SC	Qin 2016	12(984623)	RR 3.71 (2.67-5.16)*
	Single ET v SC	Grady 2012	1(15306)	RR 6.02 (2.79-13.01)*
	Frozen ET vs SC	Vermey 2018	2(607335)	OR 2.42 (0.63-9.30)
Placental abruption	ART vs SC	Qin 2016	7(95974)	RR 1.83 (1.49-2.24)*
	Single ET vs SC	Grady 2012	1(15306)	RR 0.47 (0.03-7.55)
	Frozen ET vs SC	Vermey 2018	2(607335)	OR 1.15 (0.69-1.91)
Antepartum haemorrhage	ART vs SC	Qin 2016	2(50638)	RR 2.11 (1.86-2.38)*
Pre-term labour	ART vs SC	Qin 2016	36(1422887)	RR 1.71 (1.59-1.83)*
	Donor oocyte vs SC	Storgaard 2016	2(not reported)	OR 2.30 (1.09-4.87)*
	Single ET vs SC	Pandey 2012	2(593267)	RR 1.53 (1.40-1.67)*
	Frozen ET v SC	Pandey 2012	3(39150)	RR 1.39 (1.20-1.61)*
Very pre-term labour	ART vs SC	Qin 2016	25(1381560)	RR 2.12 (1.73-2.59)*
	Single ET vs SC	Pandey 2012	2(586951)	RR 1.80 (1.4-2.24)*
	Frozen ET vs SC	Pandey 2012	3(36203)	RR 1.45 (0.98-2.13)
Small for gestation age	ART vs SC	Qin 2016	14(834861)	RR 1.35 (1.20-1.52)*
	Single ET vs SC	Grady 2012	1(15306)	RR 1.78 (0.96-3.30)
	Donor oocyte vs SC	Storgaard 2016	2(not stated)	OR 1.29 (0.91-1.83)

Low birth weight	ART vs SC	Qin 2016	36(1192602)	RR 1.61 (1.49-1.75)*
	Single ET vs SC	Pandey 2012	2(650087)	RR 1.70 (1.53-1.89)*
	Frozen ET vs SC	Pandey 2012	3(35253)	RR 1.27 (1.05-1.52)*
	Donor oocyte vs SC	Storgaard 2016	2(not stated)	OR 1.94 (1.10-3.41)*
Very low birth weight	ART vs SC	Qin 2016	30(1107410)	RR 2.12 (1.84-2.43)*
	Single ET vs SC	Pandey 2012	2(593267)	RR 1.94 (1.54-2.45)*
	Frozen ET vs SC	Pandey 2012	3(36203)	RR 1.51 (1.01-2.27)*
Postpartum haemorrhage	ART vs SC	Qin 2016	5(40183)	RR 1.29 (1.06-1.57)*
Gestational diabetes	ART vs SC	Bosdou 2020	37(1893599)	RR 1.53 (1.39-1.69)*
	Single ET vs SC	Grady 2012	1(15306)	RR 1.69 (1.19-2.42)*
Hypertensive disorder of pregnancy	ART vs SC	Pandey 2012	15(606314)	RR 1.49 (1.39-1.59)*
	Single ET vs SC	Pandey 2012	2(593267)	RR 1.58 (1.40-1.77)*
Pre-eclampsia	ART vs SC	Jackson 2004	6(219382	OR 1.55 (1.23- 1.95)
	Single ET vs SC	Grady 2012	1(15306)	RR 1.36 (0.61-3.04)
	Donor oocyte vs SC	Jeve 2016	4(10799)	OR 2.90 (1.98-4.24)*
Pregnancy induced hypertension	ART vs SC	Qin 2016	13(95600)	RR 1.30 (1.04-1.62)*
	Donor oocyte vs other ART	Masoudian 2016	6(2345)	OR 2.86 (2.10-3.90)*
Caesarean section	ART vs SC	Qin 2016	28(777545)	RR 1.58 (1.48-1.70)*
	Frozen ET vs SC	Pandey 2012	3(39150)	RR 1.76 (1.65-1.87)*
	Single ET vs SC	Pandey 2012	2(593267)	RR 1.49 (1.43-1.56)*
	Donor oocyte vs SC	Storgaard 2016	2(not stated)	OR 2.38 (2.01-2.81)*
Perinatal mortality				
Perinatal mortality	ART vs SC	Qin 2016	22(1369264)	RR 1.57 (1.46-1.70)*
	Single ET vs SC	Pandey 2012	2(593267)	RR 1.23 (0.38-4.04)

Neonatal death	Single ET vs SC	Grady 2012	1(15306)	RR 1.30 (0.08-21.33)
Admission to neonatal unit	ART vs SC	Pandey 2012	5(7628)	RR 1.58 (1.42-1.77)*
	Single ET vs SC	Grady 2012	1(15306)	RR 1.97 (0.98-3.95)
Congenital abnormalities	ART vs SC	Chen 2018	34(6764336)	RR 1.48 (1.29-1.70)*
	Donor sperm vs SC	Adams 2017	1(2933742)	RR 1.46 (1.07-2.00)*

*statistical significance

**ART: assisted reproductive technology, SC: spontaneous conception, ET: embryo transfer.

Table (3): Adverse maternal and offspring outcomes associated with assisted conception across different embryo development stages.

Outcome	Population	Systematic review	Primary studies (participants)	Risk/Odds ratio (95% confidence intervals)
Placenta previa	Blastocyst vs Cleavage	Martins 2016	3(82926)	RR 1.37 (0.88-2.13)
Abnormal placentation	Blastocyst vs Cleavage	Martins 2016	1(48158)	RR 0.99 (0.57-1.74)
Placental abruption	Blastocyst vs Cleavage	Martins 2016	4(83299)	RR 1.06 (0.68-1.64)
Antepartum haemorrhage	Frozen vs Fresh ET	Maheshwari 2018	5(63155)	RR 0.82 (0.66-1.03)
	Blastocyst vs Cleavage	Martins 2016	1(4202)	RR 0.76 (0.51-1.13)
Pre-term labour	Frozen vs Fresh ET	Maheshwari 2018	20(280622)	RR 0.90 (0.84-0.97)*
	Stimulated vs Natural Frozen ET	Kamath 2017	4(97698)	RR 1.27 (1.03-1.58)*
	Blastocyst vs Cleavage	Alviggi 2018	13(193827)	RR 1.10 (1.01-1.20)*
	Fresh Blastocyst vs Cleavage	Alviggi 2018	2(106629)	RR 1.15 (1.05-1.25)*
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 1.11 (0.99-1.25)
Very pre-term labour	Frozen vs Fresh ET	Maheshwari 2018	12(253304)	RR 0.85 (0.74-0.97)*
	Stimulated vs Natural Frozen ET	Kamath 2017	3(97493)	RR 4.22 (1.45-12.31)*
	Blastocyst vs Cleavage	Martins 2016	8(146988)	RR 1.14 (1.04-1.24)*
	Fresh Blastocyst vs Cleavage	Alviggi 2018	7(103742)	RR 1.16 (1.02-1.31)*
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 0.78 (0.57-1.07)
Small for gestation age	Frozen vs Fresh ET	Maheshwari 2018	10(142462)	RR 0.61 (0.56-0.67)*
	Stimulated vs Natural Frozen ET	Kamath 2017	1(97278)	RR 1.95 (1.03-3.67)*
	Blastocyst vs Cleavage	Alviggi 2018	7(176492)	RR 0.84 (0.76-0.92)*
	Fresh Blastocyst vs Cleavage	Alviggi 2018	5(90115)	RR 0.84 (0.76-0.94)*
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 0.59 (0.32-1.06)

Low birth weight	Frozen vs Fresh ET	Maheshwari 2018	20(280044)	RR 0.72 (0.67-0.77)*
	Stimulated vs Natural Frozen ET	Kamath 2017	4(97278)	RR 1.95 (1.03-3.67)*
	Blastocyst vs Cleavage	Alviggi 2018	11(188966)	RR 0.97 (0.90-1.04)*
	Fresh Blastocyst vs Cleavage	Alviggi 2018	8(102590)	RR 1.01 (0.94-1.10)
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 0.81 (0.58-1.14)
Very low birth weight	Frozen vs Fresh ET	Maheshwari 2018	13(260226)	RR 0.76 (0.69–0.82)*
	Stimulated vs Natural Frozen ET	Kamath 2017	2(96705)	RR 5.32 (1.04-27.18)*
	Blastocyst vs Cleavage	Alviggi 2018	7(98270	RR 0.99 (0.86-1.14)
	Fresh Blastocyst vs Cleavage	Alviggi 2018	6(55024)	RR 0.97 (0.82-1.15)
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 0.80 (0.30-2.16)
Large for gestation age	Frozen vs Fresh ET	Maheshwari 2018	7(57031)	RR 1.54 (1.48-1.61)*
	Stimulated vs Natural Frozen ET	Kamath 2017	1(364)	RR 0.94 (0.46-1.93)
	Blastocyst vs Cleavage	Alviggi 2018	5(86228)	RR 1.12 (1.03-1.21)*
	Fresh Blastocyst vs Cleavage	Alviggi 2018	4(42928)	RR 1.14 (0.97-1.35)
	Frozen Blastocyst vs Cleavage	Alviggi 2018	2(39044)	RR 1.18 (1.09-1.27)*
Postpartum haemorrhage	Blastocyst vs Cleavage	Martins 2016	2(34768)	RR 1.25 (0.85-1.84)
Gestational diabetes	Blastocyst vs Cleavage	Martins 2016	2(30939)	RR 0.76 (0.56-1.01)
Hypertensive disorder of pregnancy	Frozen vs Fresh ET	Maheshwari 2018	5(98656)	RR 1.29 (1.07-1.56)*
	Blastocyst vs Cleavage	Martins 2016	4(83299)	RR 0.96 (0.81-1.14)
Pre-eclampsia	Blastocyst vs Cleavage	Maheshwari 2013	2(13143)	RR 1.04 (0.83-1.30)
Caesarean section	Blastocyst vs Cleavage	Martins 2016	3(82926)	RR 1.05 (1.00-1.11)
Perinatal mortality	Frozen vs Fresh ET	Maheshwari 2018	12(102483)	RR 0.92 (0.78-1.08)
	Blastocyst vs Cleavage	Martins 2016	2(43278)	RR 1.48 (1.09-2.02)*

	Fresh Blastocyst vs Cleavage	Alviggi 2018	3(36666)	RR 1.35 (0.95-1.92)
	Frozen Blastocyst vs Cleavage	Alviggi 2018	1(7795)	RR 1.80 (1.07-3.01)*
Stillbirth	Frozen vs Fresh ET	Zhao 2016	6(72685)	OR 0.99 (0.65--1.24)
	Blastocyst vs Cleavage	Martins 2016	4(67680)	RR 1.08 (0.86-1.35)
	TLS vs conventional incubation	Armstrong 2019	1(76)	OR 1.00 (0.13-7.49)
Admission to neonatal unit	Frozen vs Fresh ET	Maheshwari 2018	5(19565)	RR 0.99 (0.84-1.18)
Congenital abnormalities	Stimulated vs natural cycle ET	Kamath 2017	1(205)	0.9% versus 4.3%
	Blastocyst v cleavage	Martins 2016	5(44834)	RR 0.97 (0.85-1.12)
	Frozen vs Fresh ET	Maheshwari 2018	6(133481)	RR 1.01 (0.87-1.16)

*statistical significance

**ET: embryo transfer

Table (4): Adverse maternal and offspring outcomes associated with assisted conception across different types of oocytes.

Outcome	Comparison	Systematic review	Primary studies (participants)	Risk/Odds ratio (95% confidence intervals)
Placenta previa	Donor vs autologous oocyte	Moreno 2019	4(28405)	OR 0.63 (0.33-1.20)
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	3(21115)	OR 0.53 (0.24-1.17)
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	2(7037)	OR 0.87 (0.16-4.79)
Placental abruption	Donor vs autologous oocyte	Moreno 2019	4(28405)	OR 1.15 (0.52-2.53)
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	2(20821)	OR 0.65 (0.23-2.25)
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	2(7037)	OR 1.43 (0.43-4.71)
Pre-term labour	Donor vs autologous oocyte	Moreno 2019	16(348052)	OR 1.57 (1.33-1.86)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	11(229377	OR 1.44 (1.20-1.74)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	5(37935)	OR 1.96 (1.38-2.78)*
Very pre-term labour	Donor vs autologous oocyte	Moreno 2019	6(147718)	OR 1.80 (1.51-2.15)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	5(134460)	OR 1.68 (1.10-2.59)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	3(9514)	OR 2.93 (1.65-5.20)*
Small for gestation age	Donor vs autologous oocyte	Moreno 2019	8(120100)	OR 0.83 (0.78-0.89)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	3(32606)	OR 1.19 (0.64-2.25)
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	4(36614)	OR 1.61 (1.21-2.15)*
Low birth weight	Donor vs autologous oocyte	Moreno 2019	12(257928)	OR 1.25 (1.20-1.30)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	10(220645)	OR 1.25 (1.13-1.38)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	4(36614)	OR 1.83 (1.45-2.30)*
Very low birth weight	Donor vs autologous oocyte	Moreno 2019	7(200773)	OR 1.37 (1.22-1.54)*

	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	7(194089)	OR 1.36 (1.23-1.52)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	3(9514)	OR 3.08 (1.66-5.73)*
Large for gestation age	Donor vs autologous oocyte	Moreno 2019	3(30262)	OR 0.89 (0.57-1.40)
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	2(20821)	OR 0.75 (0.20-2.81)
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	2(7037)	OR 1.13 (0.57-2.25)*
Maternal morbidity in pregnancy				
Postpartum haemorrhage	Donor vs autologous oocyte	Moreno 2019	3(28111)	OR 1.96 (1.20-3.20)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	2(20821)	OR 1.90 (0.77-4.72)
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	2(7037)	OR 1.76 (1.33-2.34)*
Gestational diabetes	Donor vs autologous oocyte	Moreno 2019	7(38289)	OR 1.27 (1.03-1.56)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	5(29499)	OR 1.28 (1.01-1.61)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	3(8358)	OR 1.12 (0.72-1.76)
Hypertensive disorder of pregnancy	Donor vs autologous oocyte	Moreno 2019	8(11049)	OR 2.63 (2.17-3.18)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	4(1203)	OR 2.62 (1.93-3.55)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	1(243)	OR 3.34 (1.52-7.36)*
Pre-eclampsia	Donor oocyte vs other ART	Masoudian 2016	15(16553)	OR 2.24 (1.42-3.53)*
	Donor vs autologous oocyte	Moreno 2019	11(54755)	OR 2.64 (2.29-3.04)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	5(29499)	OR 3.17 (2.67-3.75)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	3(8358)	OR 1.75 (1.23-2.49)*
Pregnancy induced hypertension	Donor oocyte vs other ART	Masoudian 2016	6(2345)	OR 2.86 (2.10-3.90)*
	Donor vs autologous oocyte	Moreno 2019	10(13277)	OR 2.16 (1.79-2.62)*
	Fresh donor vs Fresh autologous oocyte	Moreno 2019	2(9209)	OR 1.64 (1.26-2.13)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	2(1564)	OR 2.22 (1.43-3.46)*
Caesarean section	Donor vs autologous oocyte	Moreno 2019	7(54044)	OR 2.28 (2.14-2.42)*
	Donor vs autologous oocyte (Fresh ET)	Moreno 2019	5(32743)	OR 1.62 (1.39-1.89)*
	Donor vs autologous oocyte (Frozen ET)	Moreno 2019	3(9514)	OR 1.76 (1.54-2.01)*

*statistical significance

** ART: assisted Reproductive technology, ET: embryo transfer