

The Use of Frozen Embryo Transfer and the Development of Pregnancy-Induced Hypertension: A Literature Review

**EDITOR'S
PICK**

The Editor's Pick for this publication is the interesting review by Agbabiaka and D'Angelo, who examine the use of frozen embryo transfers (FET) and the development of pregnancy-induced hypertension. The use of frozen embryos in assisted reproduction was successfully introduced some years ago, with good outcomes in terms of pregnancy rate and live birth. However, whether pregnancy-induced complications such as hypertension and pre-eclampsia are different respect to fresh transfers is less clear. The authors, after reviewing the studies that report the incidence of hypertension and pre-eclampsia after FET, evidence a possible relation between FET and hypertension, with possible implications for clinical practice.

Elisabetta Baldi

Associate Professor of Clinical Pathology, University of Florence, Italy; Responsible of the Laboratory of Semen Analysis and Semen Bank of the University Hospital of Careggi, Florence, Italy; Responsible of the Laboratory of Assisted Reproduction of the University Hospital of Careggi, Florence, Italy.

Authors:	*Ayodele Abigail Agbabiaka, ¹ Arianna D'Angelo ^{1,2} 1. Centre for Medical Education, Cardiff University, UK 2. Wales Fertility Institute, Swansea Bay University Health Board, Cardiff, UK *Correspondence to Agbabiakaaa@cardiff.ac.uk
Disclosure:	The authors have declared no conflicts of interest.
Received:	28.10.20
Accepted:	04.06.21
Keywords:	Assisted conception, embryo transfer, frozen embryo transfer (FET), gestational hypertension, pre-eclampsia, pregnancy-induced hypertension (PIH).
Citation:	EMJ Repro Health. 2021;7[1]:44-53.

Abstract

The use of assisted reproduction techniques has been associated with obstetric complications. An understanding about which methods and treatment protocols produce better outcomes would provide greater opportunities for a successful pregnancy. The aim of this literature review was to identify whether frozen embryo transfer (FET) leads to a greater incidence of pregnancy-induced hypertension (PIH) compared to fresh embryo transfer. Fifteen studies were identified and subsequently reviewed. Eleven studies suggested FET increased the incidence of PIH-gestational hypertension and pre-eclampsia. The evidence suggests a correlation between FET and PIH. Exploration into why this is the case should be the focus of future studies. Implications for clinical practice involve extensive preconception counselling and potentially advising prophylactic low-dose aspirin with the aim of lower the incidence of PIH.

INTRODUCTION

Subfertility affects 1/6-7 couples worldwide.¹ Assisted reproduction techniques such as *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are treatment options for these couples. Hypertension-related disorders affect 8-10% of pregnancies in the UK.² It can cause fatal consequences, such as premature labour and intrauterine growth restriction, and maternal consequences, e.g., liver damage and stroke.³ Using fresh or frozen embryos are both options for IVF/ICSI under the National Institute for Health and Care Excellence (NICE) guidelines.¹ The Human Fertilisation and Embryology Authority (HFEA)⁴ reports approximately one-third of IVF/ICSI cycles result in frozen embryos. It would be beneficial to better understand the effect of frozen embryo transfer (FET) related to obstetric outcomes so that optimal care can be provided. A literature review was performed to assess the current evidence to determine whether FET leads to a greater rate of pregnancy-induced hypertension (PIH), e.g., pre-eclampsia (PE) and gestational hypertension (GH). The objective of this review was to identify whether FET use in IVF/ICSI leads to a greater incidence of PIH, specifically, PE and GH, compared to when fresh embryo transfer (ET) is used.

METHOD

Objective

To identify whether FET use in IVF/ICSI leads to a greater incidence of PIH, specifically PE and GH, compared to when fresh ET is used.

Outcomes

The primary outcome was the development of PIH, to include GH and PE.

A Medline search was performed from inception until April 2020. The following search terms were used: “assisted reproductive techniques”, “assisted reproductive treatment”, “assisted reproductive technology”, “*in vitro* fertilisation”, “IVF-ET”, “embryo transfer”, “intracytoplasmic sperm injections”, “oocyte donation”, and “sperm donation” alongside “pre-eclampsia”, “pregnancy induced hypertension”, “gestational hypertension”, and “eclampsia”, alongside

“cryopreservation”, “vitrification”, “fresh embryo”, “frozen embryo”, “frozen blastocyst”, and “blastocyst vitrification”.

Sixty articles were found and screened by reading the title and abstracts. Studies that compared the use of FET and fresh ET and the development of PIH were selected. Inclusion criteria for the selected studies were English-language papers, human studies, randomised controlled trials (RCT), cohort studies, case-control studies, retrospective, and prospective studies. Exclusion criteria were systemic reviews/meta-analysis, letters to the editor, and case reports/abstracts proceedings (grey literature). Nineteen articles were included in the final analysis. The screening process is summarised in [Figure 1](#).

RESULTS

Following the search, 19 articles were retrieved in full, and four were excluded because they did not have the appropriate data or analysis comparing FET and fresh ET ([Figure 1](#)). Fifteen articles fulfilled the inclusion criteria. [Tables 1 and 2](#) outline the study type, main results, and comments about the included articles. [Table 1](#) includes articles relating to PE and GH as separate outcomes.

[Table 2](#) includes articles relating to PIH and hypertensive disorders in pregnancy as a single outcome. PIH includes GH, PE, and eclampsia. Hypertensive disorders in pregnancy refer to conditions associated with PIH, as well as pre-existing hypertension complicating pregnancy.

Of the 15 articles reviewed, summarised in [Tables 1 and 2](#), a majority (11/15) of papers found that FET confers a higher risk of developing PIH.^{6-9,13-19} Chen et al.⁷ and Wei et al.¹³ found an increased incidence of PE but not GH in the FET group. After adjusting for maternal age, BMI, parity, multiple gestations, and smoking, excluding donor oocytes, the results were consistent ([Tables 1 and 2](#)). Imudia et al.⁵ found that fresh ET conferred a higher risk of PE compared to FET.

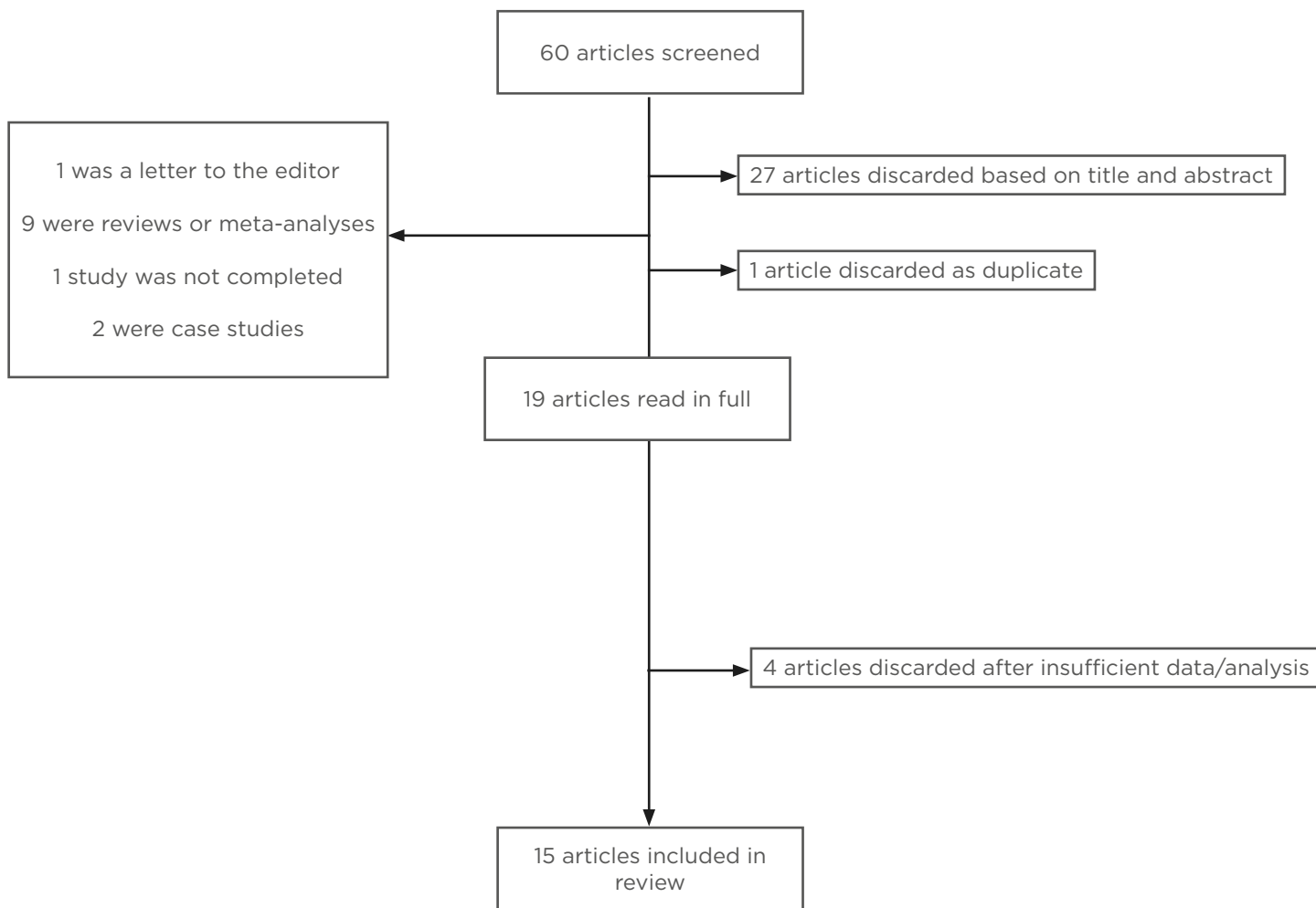


Figure 1: Screening process of articles after keyword search.

Table 1: Study characteristics and incidence of pre-eclampsia and gestational hypertension.

Publication	Study design	Population (fresh versus frozen)	HRT or natural cycle	Outcome measure	Results (95% CI)	Comments
Imudia et al. ⁵	Retrospective single-centre cohort study	32 versus 20	HRT	PE	22% (fresh) versus 0% (frozen); p=0.04	Only singleton pregnancies and patients with high peak oestrogens. Adjusted for BMI, antral follicle count, and peak serum oestrogen level

Table 1 continued.

Publication	Study design	Population (fresh versus frozen)	HRT or natural cycle	Outcome measure	Results (95% CI)	Comments
Barsky et al. ⁶	Retrospective single-centre cohort study	289 versus 109	HRT	PE	aOR: 3.1 (1.2–8.4); p=0.023	Adjusted for maternal age, newborn sex, diabetes status, and parity. Singleton pregnancies and autologous oocytes only
Chen et al. ⁷	Multicentre RCT	762 versus 746	HRT	GH	Rate ratio: 1.97 (0.68–5.71); p=0.20	Exclusively patients with PCOS.
				PE	Rate ratio: 3.12 (1.26–7.73); p=0.009	Adjusted for study site and baseline characteristics, e.g., maternal age, BMI
Jing et al. ⁸	Retrospective single-centre cohort study	129 versus 188	Not specified	GH	aOR: 4.85 (1.34–17.46)	Adjusted for maternal age, BMI, parity, twins, neonatal sex, and number of embryos transferred. FET versus fresh ET not the only variable being studied; also comparing stage of embryo biopsy. FET with blastocyst biopsy, and fresh ET with cleavage biopsy
Sites et al. ⁹	Retrospective multicentre cohort study	13,976 versus 1,961	Not specified	PE	Singleton and autologous eggs aOR: 2.17 (1.67–2.82); p<0.0001	Adjusted for BMI (missing >50% of the data), maternal age, maternal race, diabetes, parity, HTN, infant sex, and birth year. Unadjusted p values with results concerning GH, twins, and donor oocytes

Table 1 continued.

Publication	Study design	Population (fresh versus frozen)	HRT or natural cycle	Outcome measure	Results (95% CI)	Comments
Xiong et al. ¹⁰	Single-centre retrospective cohort study	446 versus 212	Both	GH	OR: 0.44 (0.13–1.34); aOR: 0.49 (0.15–1.51)	Adjusted for maternal age, BMI, and infertility years
				PE	OR: 0.93 (0.42–1.96); aOR: 0.98 (0.44–2.12)	
Blazquez et al. ¹¹	Retrospective single-centre cohort study	353 versus 80	HRT	GH	aOR: 1.45 (0.75–2.81); p=0.27	Only donated oocytes. Adjusted for maternal age, BMI, primigravity, and multiple pregnancy
				Preterm PE	aOR: 1.95 (0.72–5.26); p=0.18	
				Term PE	aOR: 0.30 (0.04–2.35); p=0.25	
Lei et al. ¹²	Retrospective single-centre cohort study	1,583 versus 673	Not specified	GH	10.2% (fresh) versus 10.0% (frozen)	Autologous eggs. No aOR provided for fresh ET versus FET. No p value provided for fresh ET versus FET
				Mild PE	3.3% (fresh) versus 3.0% (frozen)	
				Severe PE	1.3% (fresh) versus 1.3% (frozen)	
Wei et al. ¹³	Multicentre RCT	401 versus 512	Both	GH	RR: 1.27 (0.53–3.04); p=0.59	Extensive exclusion criteria. Singleton pregnancies only
				PE	RR: 3.13 (1.06–9.30); p=0.029	

aOR: adjusted odds ratio; ART: assisted reproduction technique; CI: confidence interval; ET: embryo transfer; FET: frozen embryo transfer; GH: gestational hypertension; HTN: hypertension; HRT: hormone replacement therapy; OR: odds ratio; PCOS: polycystic ovarian syndrome; PE: pre-eclampsia; RCT: randomised controlled trial; RR: relative risk.

Table 2: Study characteristics and incidence of pregnancy-induced hypertension and hypertensive disorders in pregnancy.

Publication	Study design	Population (fresh versus frozen)	HRT or natural cycle	Outcome measure	Results (95% CI)	Comments
Ishihara et al. ¹⁴	Retrospective nationwide cohort study	18,478 versus 34,545	Not specified	PIH	aOR: 1.58 (1.35–1.86); p<0.001	Only autologous oocytes and singleton pregnancies. Adjusted for maternal age and sex of infant
Opdahl et al. ¹⁵	Retrospective multi-country cohort study	49,560 versus 7,493	Not specified	Hypertensive disorders in pregnancy	Singleton aOR: 1.24 (1.11–1.37)	Adjusted for parity, maternal age, birth year, country, and offspring sex. Able to compare FET versus fresh ET in same mother
					Twins aOR: 1.72 (1.45–2.04)	
					Same mother OR: 1.60 (1.12–2.28); aOR: 2.63 (1.73–3.99)	
Belva et al. ¹⁶	Retrospective single-centre cohort study	1,517 versus 912	Natural cycle (majority)	PIH	7.2% (fresh) versus 13.4% (frozen); p=0.0001	Adjusted for number of embryos transferred, embryo stage at transfer/day of transfer, maternal age (significantly higher in vitrified group), BMI, parity, and smoking
Ginström Ernstad et al. ¹⁷	Retrospective multicentre study	24,365 versus 9,726	Both	PIH	OR: 1.33 (1.21–1.47); aOR: 1.51 (1.35–1.68)	Adjusted for maternal age, BMI, parity, year of birth, smoking, chronic HTN, infant sex, maternal education, cause of infertility, years of infertility, freezing method, culture duration, ART method, and number of gestational sacs. Singleton pregnancies. Autologous oocytes only.

Table 2 continued.

Publication	Study design	Population (fresh versus frozen)	HRT or natural cycle	Outcome measure	Results (95% CI)	Comments
Ginström Ernstad et al. ¹⁸	Retrospective cohort multicentre study	4,459 versus 3,659	Not specified	PIH	OR: 1.39 (1.16–1.67); aOR: 1.47 (1.19–1.81)	Adjusted for country, year of birth, maternal age, BMI, parity, smoking, number of gestational sacs, parental education, ART method, and child sex. Singleton pregnancies. Autologous oocytes only
Luke et al. ¹⁹	Retrospective multicentre cohort study	62,192 versus 21,390	Not specified	PIH	Autologous oocytes aOR: 1.30 (1.20–1.40) Donor oocytes aOR: 1.70 (1.47–1.96)	Adjusted for BMI, maternal age, race/ethnicity, parity, education, country, state, year of birth, infant sex, and cause of infertility. Singleton pregnancies only

aOR: adjusted odds ratio; ART: assisted reproduction technique; CI: confidence interval; ET: embryo transfer; FET: frozen embryo transfer; HTN: hypertension; HRT: hormone replacement therapy; OR: odds ratio; PIH: pregnancy-induced hypertension; RR: relative risk.

DISCUSSION

The results suggest that FET increases the incidence of PIH. A variety of studies display this correlation, including RCTs. Each study focussed on different elements and populations giving validation to this claim. The main limitations of these results are the quality of the evidence presented.

Risk Factors of Pre-eclampsia

When looking at the evidence presented, the impact of confounders on the results must be considered, such as risk factors

for PE, which include older age, multiple gestation, BMI, past medical history (PMH) of PE, diabetes, family history of PE, and parity.^{20,21}

Most of the studies had information on risk factors and adjusted their results accordingly (Tables 1 and 2), finding consistent results. However, most of the studies did not adjust for PMH,^{5-12,14-19} which is a significant risk factor for PIH. Bartsch et al.,²⁰ who conducted a meta-analysis of over 90 studies, found that PMH of PE increased the risk of developing PE in subsequent pregnancies by eight times. The same study found that pre-gestational diabetes almost quadrupled the risk of developing

PE.²⁰ Nonetheless, the studies that adjusted for or excluded pre-gestational diabetes still found that FET increased the risk of developing PIH.^{6,9,19}

IVF/ICSI is a complex process with many variables that may factor into the development of PIH. This information was not always accounted for.^{6,9,10,14,15,17-19} Embryo biopsy for pre-implantation genetic testing and donor oocytes have been associated with significantly increased risk of PIH.²²⁻²⁴ However, studies excluding donor oocytes still had an increased risk of PIH during FET.^{6,9,14,17-19}

Natural versus Hormone Replacement Therapy Cycle in Frozen Embryo Transfer

A potential factor in developing PIH during FET is the type of endometrial preparation used for the FET cycle: natural versus hormone replacement therapy (HRT). Of the 15 articles reviewed, eight commented on the method used for endometrial preparation (Tables 1 and 2). This is a confounding factor that most studies have not adjusted for (Tables 1 and 2). A specific analysis comparing HRT versus natural cycles in FET found that HRT cycles lead to an increased risk of PIH compared to natural cycles, adjusted odds ratio 1.78,¹⁷ suggesting a role for HRT in the development of PIH.

The mechanism by which HRT cycles, commonly used in FET, increase the risk of PIH is still debated. A suggested mechanism is the absence of the corpus luteum (CL), a feature of HRT cycles; subsequently, the absence of hormones produced by the CL could adversely affect the maternal cardiovascular system.^{25,26} von Versen-Höyneck et al.²⁶ found that HRT with no CL had a significantly higher incidence of PE compared to natural FET with one CL.

Study Type

The study type will contribute to the quality of the evidence. The majority of the papers were retrospective cohort studies (Tables 1 and 2). One of the major limitations is that information on confounding factors may not be available. Another disadvantage is that any missing information deemed important would be difficult to find and follow up. However, retrospective cohort studies have the advantage of low risk of response bias because individuals did not

know what the data would be used for, and large sample sizes, which allow studies to be more representative of the general population.

The highest-quality evidence comes from RCTs. RCTs reduce the risk of selection bias because participants are randomly assigned to each group. Unfortunately, these trials were not double-blinded, and in this circumstance, may not be ethically possible. RCTs are able to control a variety of potential confounders. Both of the RCTs found an increased risk of PE when FET was used, but GH incidence was not affected.^{7,13}

Multicentre studies have the added benefit of reduced selection bias because of the wider range of participants available, and allow conclusions to be made with regard to a larger patient base (Tables 1 and 2). However, there is a risk of performance bias because the patients are more likely to have differences in their prenatal/antenatal care and treatment. Some of the studies had a wide date period of 10+ years.^{15,17-19} This leads to an extensive sample size, reducing selection bias; however, it can expose the study to unknown confounders because medical practices and lifestyle can change during that time period.

A Nordic study¹⁵ found in the same mother the chance of developing PIH was increased by 2.5 times when using FET compared to fresh ET.¹⁵ This is strong evidence because many maternal confounding factors can be removed with this model, suggesting the correlation between FET and PIH is not solely due to maternal factors. However, the sample size for this analysis was small.

All four of these papers that did not see a correlation between PIH and FET are single-centre studies.^{5,10-12} The advantage is that there is a reduced risk of confounders associated with variation of prenatal/antenatal care and guidelines affecting the results. However, they are more likely to have smaller sample sizes.^{5,11} The four studies had an increased risk for Type 2 error, where a difference in treatment outcome is not seen but there is one present, because of a significantly smaller sample size in the FET versus fresh ET group. Blazquez et al.¹¹ had a wide confidence interval, which makes it difficult to interpret where the true odds lie. The evidence provided by Lei et al.¹² is limited because of a lack of statistical data, i.e., the p value.

Previous Studies

Previous reviews and meta-analyses have also found an increase of PIH in patients with FET.²⁷⁻²⁹ Maheshwari et al.²⁷ included five studies in their meta-analysis and found FET led to a 29% increased risk of PIH (relative risk [RR]: 1.29). Similarly, Sha et al.²⁸ reviewed seven studies and found a 44% increased risk of developing PIH when using FET (RR: 1.44) in relation to PIH development. However, these reviews also showed a lower risk of other obstetric complications, e.g., preterm delivery, placenta praevia, and placental abruption.^{27,28} This suggests there is a role for FET and that special considerations should be taken when comparing the options.

Clinical Implications

Clinically, these data suggest a possible use of preventative treatment, e.g., low-dose aspirin during FET in high-risk individuals. The efficacy of aspirin in preventing PE has been replicated in >70 trials and reduces the risk of developing PE by 18% (RR: 0.82).³⁰

NICE³¹ recommend that patients with risk factors take aspirin daily from the 12th week of gestation. Based on the evidence presented, there may be a role for including FET as a risk factor. Compared with other risk factors, such as PMH or family history of PE, the chance of developing PE with FET may not be increased as

dramatically. However, in the setting of assisted reproduction techniques, where there are often limited chances, it seems worth investigating a role for prophylaxis. Clinicians should consider their use of FET when weighing up the risk of PIH and monitor patients more closely.

CONCLUSION

This literature review comparing the effect of FET and fresh ET on development of PIH shows there is an association between FET and PIH. There was a large number of articles¹⁵ reviewed, including two RCTs, compared with previous reviews, which included only 2-7 articles and were limited to only observational studies.²⁷⁻²⁹ This review could highlight a role for use of preventative treatment during FET in high-risk individuals. It also suggests the importance of providing appropriate counselling during the FET cycle and potential referral for antenatal counselling when other risk factors are associated. This is the first review to discuss the potential use of aspirin in FET. Though there is a correlation established, future studies exploring the reasons for FET conferring a greater risk are needed. This could be due to embryo quality following the cryopreservation and thawing procedures or different intrauterine environment, e.g., absence of the CL,^{17,25} or ultimately, to the hormonal treatment and protocols associated with FET.¹⁵

References

1. National Institute for Health and Care Excellence. Fertility Problems: Assessment and Management. 2017. Available at: <https://www.nice.org.uk/guidance/cg156/ifp/chapter/Fertility-problems>. Last accessed: 28 April 2021.
2. National Institute for Health and Care Excellence. Hypertension in Pregnancy. 2019. Available from: <https://cks.nice.org.uk/hypertension-in-pregnancy#!backgroundSub:1>. Last accessed: 28 April 2021.
3. British Medical Journal B. Pre-eclampsia. 2020. Available at: <https://bestpractice.bmj.com/topics/en-gb/326>. Last accessed: 28 April 2021.
4. Human Fertilisation and Embryology Authority. Embryo Freezing. 2019. Available from: <https://www.hfea.gov.uk/treatments/fertility-preservation/embryo-freezing/>. Last accessed: 28 April 2021.
5. Imudia AN et al. Elective cryopreservation of all embryos with subsequent cryothaw embryo transfer in patients at risk for ovarian hyperstimulation syndrome reduces the risk of adverse obstetric outcomes: a preliminary study. *Fertil Steril*. 2013;99(1):168-73.
6. Barsky M et al. Are perinatal outcomes affected by blastocyst vitrification and warming? *Am J Obstet Gynecol*. 2016;215(5):603.e1-5.
7. Chen ZJ et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2016;375(6):523-33.
8. Jing S et al. Obstetric and neonatal outcomes in blastocyst-stage biopsy with frozen embryo transfer and cleavage-stage biopsy with fresh embryo transfer after preimplantation genetic diagnosis/screening. *Fertil Steril*. 2016;106(1):105-12.e4.
9. Sites CK et al. Embryo cryopreservation and preeclampsia risk. *Fertil Steril*. 2017;108(5):784-90.
10. Xiong F et al. Correlation of hypertensive disorders in pregnancy with procedures of *in vitro* fertilization and pregnancy outcomes. *Experimental Ther*. 2017;14(6):5405-10.
11. Blazquez A et al. Risk of pre-eclampsia after fresh or frozen embryo transfer in patients undergoing oocyte donation. *Eur J Obstet Gynecol Reprod Biol*. 2018;227:27-31.

12. Lei LL et al. Perinatal complications and live-birth outcomes following assisted reproductive technology: a retrospective cohort study. *Chin Med J*. 2019;132(20):2408-16.
13. Wei D et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet*. 2019;393(10178):1310-8.
14. Ishihara O et al. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. *Fertil Steril*. 2014;101(1):128-33.
15. Opdahl S et al. Risk of hypertensive disorders in pregnancies following assisted reproductive technology: a cohort study from the CoNARTaS group. *Hum Reprod*. 2015;30(7):1724-31.
16. Belva F et al. Neonatal health including congenital malformation risk of 1072 children born after vitrified embryo transfer. *Hum Reprod*. 2016;31(7):1610-20.
17. Ginström Ernstad E et al. Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. *Am J Obstet Gynecol*. 2019;221(2):126.e1-e18.
18. Ginström Ernstad E et al. Perinatal and maternal outcome after vitrification of blastocysts: a Nordic study in singletons from the CoNARTaS group. *Hum Reprod*. 2019;34(11):2282-9.
19. Luke B et al. *In vitro* fertilization and risk for hypertensive disorders of pregnancy: associations with treatment parameters. *Am J Obstet Gynecol*. 2020;222(4):350.e1-e13.
20. Bartsch E et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ*. 2016;353:i1753.
21. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*. 2005;330(7491):565.
22. Zhang WY et al. Maternal and neonatal outcomes associated with trophectoderm biopsy. *Fertil Steril*. 2019;112(2):283-90.e2.
23. Salha O et al. The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. *Hum Reprod*. 1999;14(9):2268-73.
24. Blazquez A et al. Is oocyte donation a risk factor for preeclampsia? A systematic review and meta-analysis. *J Assist Reprod Genet*. 2016;33(7):855-63.
25. von Versen-Höynck F et al. Increased preeclampsia risk and reduced aortic compliance with *in vitro* fertilization cycles in the absence of a corpus luteum. *Hypertension*. 2019;73(3):640-9.
26. von Versen-Höynck F et al. Absent or excessive corpus luteum number is associated with altered maternal vascular health in early pregnancy. *Hypertension*. 2019;73(3):680-90.
27. Maheshwari A et al. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? *Hum Reprod Update*. 2018;24(1):35-58.
28. Sha T et al. Pregnancy-related complications and perinatal outcomes resulting from transfer of cryopreserved versus fresh embryos *in vitro* fertilization: a meta-analysis. *Fertil Steril*. 2018;109(2):330-42.e9.
29. Roque M et al. Obstetric outcomes after fresh versus frozen-thawed embryo transfers: A systematic review and meta-analysis. *JBRA assisted reproduction*. 2018;22(3):253.
30. Duley L et al. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2019;2019(10):CD004659.
31. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. 2019. Available at: <https://www.nice.org.uk/guidance/ng133/chapter/Recommendations#reducing-the-risk-of-hypertensive-disorders-in-pregnancy>. Last accessed: 28 May 2021.

FOR REPRINT QUERIES PLEASE CONTACT: INFO@EMJREVIEWS.COM