Acute cardiovascular changes in women undergoing in vitro fertilisation (IVF), a systematic review and meta-analysis

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ABSTRACT

Objectives: Ovarian stimulation during fertility treatment leads to profound maternal physiological changes. Women undergoing in vitro fertilisation (IVF) may be at an increased risk of future cardiovascular morbidity, though little is known about the effects on maternal cardiovascular function. We aim to systematically review whether IVF treatment is associated with changes in maternal haemodynamic parameters, and the effects of different protocols.

Study Design: A systematic review and meta-analysis of English language studies identified on Medline and EMBASE database, between 1978, to 2019. Search terms: IVF, maternal haemodynamics, and cardiovascular. Studies reporting on ovulation induction, intrauterine insemination, and oocyte donation were excluded. Methodological quality was assessed by using the adapted Critical Appraisal Skills Programme (CASP) checklist. A meta-analysis was conducted for blood pressure and heart rate on patients undergoing the long GnRH agonist protocol according to Cochrane guidelines. We considered four time points in the IVF cycle, in chronological order: pre-treatment, pituitary down regulation, peak oestradiol and the luteal phase.

Results: Nine suitable studies were identified; four fulfilled the criteria for meta-analysis. Two studies measuring heart rate found a significant increase in heart rate from pituitary down-regulation to peak estradiol levels, which was supported by the meta-analysis (3.78 ± 2.18 *($p = < 0.0001$)*). Three studies reported a significant decrease in blood pressure from baseline, with those suitable for meta-analysis showing a significant decrease in mean arterial pressure (-2.08 ± 1.79 *($p = < 0.0001$)*). Cardiac functional changes were reported for all studies and the changes depended on the type of protocol used.

Conclusions: In Vitro Fertilisation leads to acute changes in maternal haemodynamics at different time points of the stimulation protocol. We found an increase in heart rate from pituitary down-regulation to peak estradiol levels and a significant decrease in blood pressure from baseline or pituitary down-regulation to the luteal phase. Cardiac functional changes were reported for all studies on the agonist protocol, but no significant changes were found using the antagonist protocol. It remains unclear as to whether these acute changes were associated with pregnancy complications or chronic cardiovascular sequelae.

Introduction

Increasing numbers of women seek assisted reproductive techniques in the U.K. and worldwide [1,2], they are frequently older and may have pre-existing cardiovascular risk factors and morbidities [3]. Though in vitro fertilisation (IVF) requires the administration of stimulating hormones which induce supra-physiological levels of reproductive hormones, there is little understanding of how these changes acutely influence maternal haemodynamics or the outcome of a resulting pregnancy.

Spontaneously conceived pregnancies may be a useful model to represent hemodynamic adaptations in the presence of increasing levels of reproductive hormones. From the first trimester of pregnancy, peripheral vascular resistance falls, cardiac output

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increases and there is a fall in systolic and diastolic blood pressure [4]. However, the hormonal changes during the first weeks of early pregnancy cannot be equated with the rapid changes observed within a few days during IVF. IVF cycles are associated with systemic conditions such as ovarian hyperstimulation syndrome and rarer cardiovascular complications such as coronary dissection in a woman with no history of prior cardiovascular disease [5] [6]

Pregnancies conceived through assisted conception in general are thought to be associated with obstetric complications such as HDP [7], PE and small for gestational age (SGA) [8,9]. However, it still remains unclear whether the causative factor is the treatment itself, or pre-existing maternal characteristics, as for example maternal age [10,11].

Large retrospective cohort studies are inconsistent regarding risk of long-term cardiovascular morbidity in fertility therapy. A meta-analysis by Dayan et al. found a weak but potential risk of stroke 8–9 years later in women who have undergone assisted conception, although IVF was not stratified amongst other reproductive therapies, such as intrauterine insemination or ovulation induction [12]. It is still unknown whether hormonal changes during IVF treatment, the long-term effects of obstetric complications, or the inherent maternal risk factors in the subpopulation of IVF users, or which of these factors may lead to an increased risk of cardiovascular complications.

The objective of this study is to systematically review changes in the maternal hemodynamic parameters, heart rate, blood pressure, cardiac structure and function, in women undergoing IVF treatment.

Materials and methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for systematic reviews was adhered to [13]. The inclusion and exclusion criteria were pre-defined before the literature search was conducted. The study protocol was registered at PROSPERO International Prospective Register for systematic reviews (CRD42018112610).

Data sources and search strategy

Studies were identified on the electronic database Medline and EMBASE, covering the period from 1978 to August 2018. The search was limited to human studies and those written in English language only. Further studies were identified by examining the references of relevant studies. The detailed search terms were made with assistance from the health science librarian (***Supplemental Methods 1).***

Study selection

Studies identified through the literature search were uploaded onto a programmed Excel document. Two reviewers (E.F. and R.J.) screened the title and abstracts of the papers against pre-defined inclusion criteria. Full text screening was also conducted by the two reviewers. Disagreement was resolved through discussion with the supervisor (C.L.), and reasons for exclusion were recorded.

Eligibility criteria

We included longitudinal studies of patients undergoing IVF treatment which studied the outcomes of interest. We excluded narrative reviews, animal studies, and case studies.

The intervention was defined as IVF, intracytoplasmic sperm injection (ICSI), frozen cycles, fresh cycles, fresh embryo transfers, single embryo transfers, and multiple embryo transfers. We included studies reporting both agonist and antagonist protocols. We excluded studies which used a different assisted conception method, such as clomiphene ovulation induction, intrauterine insemination, and oocyte donation.

Stringent exclusion criteria were applied for the meta-analysis; agonist protocol studies with clearly defined timings of hormone administration. This was to reduce heterogeneity between the studies by accounting for variations in methodology. The antagonist protocol was not included in the meta-analysis due to the lack of studies available.

Outcome measures

Maternal blood pressure, heart rate, cardiac output, and cardiac functional and structural measurement (e.g. cardiac output/ heart rate variability/Right and left ventricular end diastolic function/ ejection fraction) from cardiac echocardiography.

Data extraction

Data extraction for the outcomes were conducted using a bespoke excel table by two authors (E.F. and R.J.). Extracted data included details of IVF treatment (fertility medications, date of oocyte transfer, number of oocytes transferred) and patient demographic information (age, parity, reason for infertility).

Data analysis

The changes in blood pressure, heart rate, or cardiac function and structure which took place during the following time points were recorded; baseline measurements before starting IVF treatment, confirmation of pituitary down-regulation, peak serum estradiol levels after ovarian stimulation, and luteal phase after oocyte collection (Fig. 1).

For heart rate and blood pressure, the trend in change between each time point was summarized with the vector of change (up/ down arrow), and statistical significance was noted. For cardiac structural and functional changes, a narrative summary was conducted due to the large heterogeneity between the modes of measurements taken.

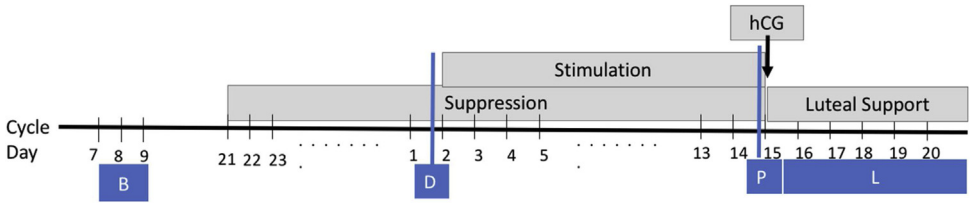

Fig. 1. Shows measurement time points taken during the long GnRH agonist protocol. Baseline (B) indicates the mid-follicular phase before any hormonal treatment has begun, Pituitary downregulation (D), Peak Oestradiol levels after stimulation (P), and Luteal phase (L) after hCG injection and oocyte retrieval.

Meta-Analysis

A meta-analysis of eligible studies was synthesized for blood pressure and heart rate, for patients undergoing the agonist protocol. A mean and standard deviation (SD) was generated for the cardiovascular parameters for each time point mentioned above, by combining the values of eligible studies. The difference between the means for each time point was calculated from the Cochrane guidelines under the hypothesis that the correlation is 1 [14].

Quality assessment

The assessment for bias was conducted by two authors. An adapted Critical Appraisal Skills Programme (CASP) checklist was used to assess for the risk of bias (***Supplemental Methods 2***). Studies that were deemed to be very low to low quality were assessed for exclusion.

Results

Result of search

The extensive literature search yielded 2079 unduplicated studies. 306 studies were excluded after the removal of duplicates, and 1773 studies underwent title and abstract screening. Of these, 150 studies were included for full text screening. Fig. 2. displays the screening process for the inclusion and exclusion criteria and the characteristics of the included studies are presented in ***Supplemental*** Table 1.

In total, nine longitudinal studies were included in the review. Protocols used were the Antagonist protocol (n = 3) and the Agonist protocol (n = 7).

Systematic review

Heart rate

Five studies reported changes in heart rate over the IVF protocol. Two studies on the agonist protocol demonstrated a significant increase in heart rate between pituitary down regulation to peak oestradiol levels [15,16]. However, two studies, including one on the GnRH antagonist protocol, demonstrated no significant change in heart rate (Table 1) from pituitary down regulation to peak estradiol levels. One study did not comment on significant changes [17].

Two studies considered the change in heart rate from pituitary downregulation to the luteal phase. There were no significant changes found between pituitary downregulation and 8 days post

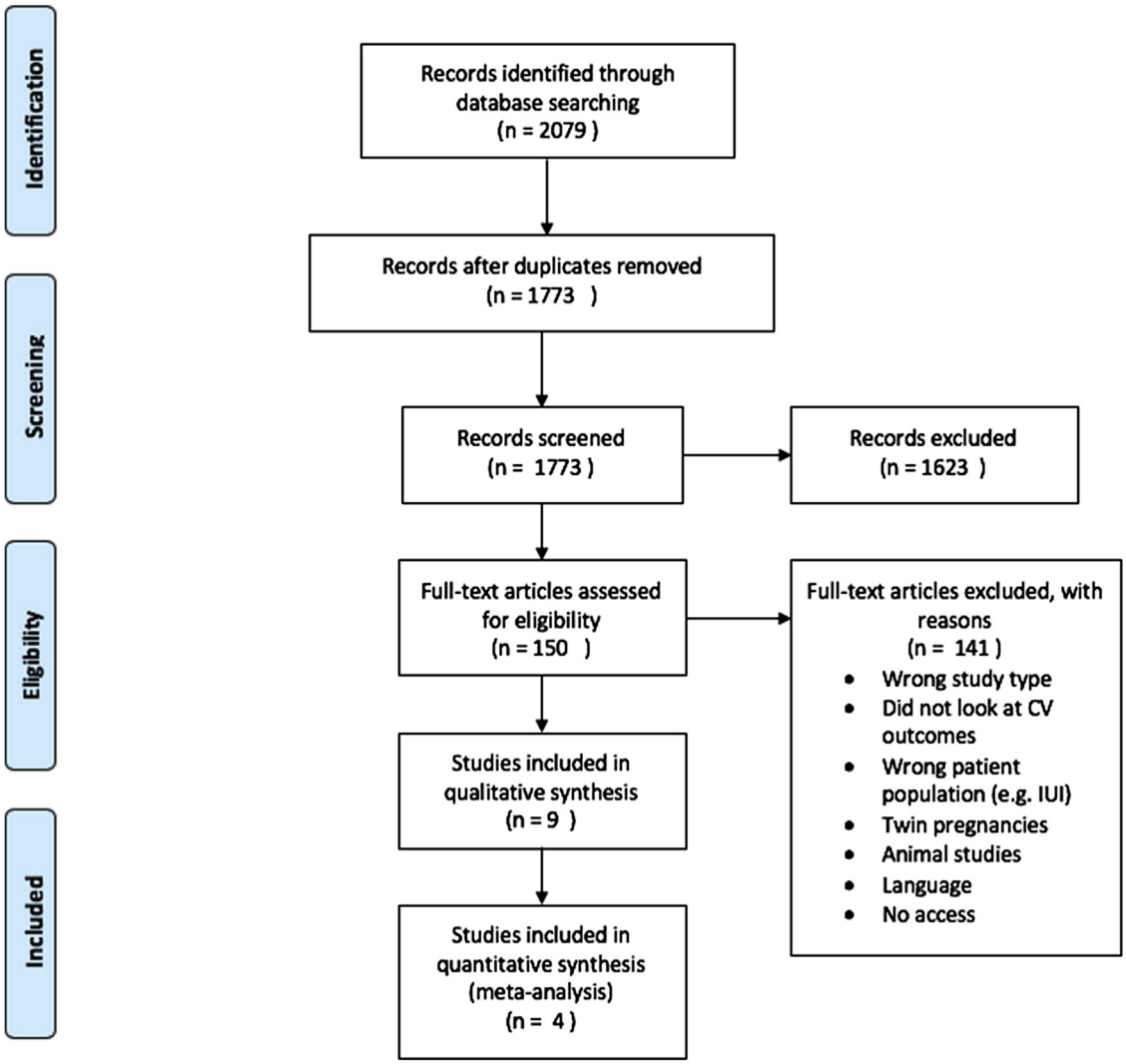

Fig. 2. PRISMA flow diagram showing study selection process for identified papers.

Table 1
Summary of changes in heart rate during IVF protocol.

Study	Protocol	Change in Heart Rate
La Sala (1989)	Long GnRH[a] agonist	Significant increase from pituitary downregulation to peak estradiol levels. No significant changes from pituitary downregulation to 12 days after gamete-intrafallopian tube transfer in both women who conceived and did not conceive.
Nevo (2007)	Long GnRH agonist	Significant increase from pituitary downregulation to peak estradiol levels. No significant changes from pituitary downregulation to 8–9 days after hCG[b] administration
Weissman (2008)	Long GnRH agonist	No significant change from pituitary downregulation to peak estradiol levels.
Li (2013)	Long GnRH agonist	Did not comment on significance from pituitary downregulation to peak estradiol levels. Did not comment on significant changes from downregulation to luteal phase (day 7 post-oocyte pick up or 16 after embryo transfer)
Ucukuyu (2010)	GnRH antagonist	No significant change noted from day 2 of cycle (baseline) to peak estradiol levels (day of hCG administration).

[a] GnRH (gonadotrophin releasing hormone).
[b] hCG (human chorionic gonadotrophin).

human chorionic gonadotrophin (hCG) injection, or 12 days after gamete intrafallopian tube transfer [15,16].

Blood pressure

Seven studies reported changes in systolic, diastolic, and mean arterial blood pressure (SBP, DBP, MAP) (Table 2) during the IVF protocol:

Two studies compared baseline MAP from the mid-luteal or mid-follicular phase of a spontaneous menstrual cycle to pituitary downregulation [18,19]. One study found a significant increase in MAP, whereas the other did not find a significant difference, respectively.

Six studies reported changes from baseline levels or pituitary down-regulation to peak oestradiol levels. Three studies on the agonist protocol found a significant decrease in MAP [15] [19] [18], and one study on the antagonist protocol found a significant decrease in SBP and DBP [20]. One study on the agonist protocol found no change in MAP from pituitary down-regulation to peak oestradiol levels [16], and one study on the agonist protocol did not comment on significant changes [17].

Six studies reported on changes from baseline or pituitary downregulation to the luteal phase after hCG injection. Three studies found a significant decrease in MAP from baseline before starting hormonal treatment, to the luteal phase (day 7 or 11 after hCG injection) [21,19,18]. From pituitary downregulation to the luteal phase (12 days after GIFT), one study found a significant decrease in MAP, SBP, and DBP in women who conceived, whereas in the same study, a significant difference was not found in women who did not conceive [15]. One study did not find any significant changes in MAP during this time period (pituitary downregulation to 8–9 days post hCG injection), and one study did not comment on significant changes [20].

Cardiac function

Five studies reported the cardiac functional and structural changes during the IVF protocol. Two studies on the agonist protocol reported a significant increase in cardiac output or cardiac index from pituitary downregulation or baseline to peak estradiol levels (Table 3) [15,18].

One study reported an increase in left ventricular end-diastolic volume (LVEDV) and a decrease in left ventricular ejection fraction (LVEF) during the agonist protocol, when comparing pituitary downregulation measurements to the luteal phase (Day 7 after oocyte retrieval)(Li et al.,2012). No significant changes to cardiac structure were found. However, by 16 days post embryo transfer, LVEDV decreased in both women who conceived and women who did not, and there was no significant difference in LVEF between the two groups [17].

Uckuyu et al. reported patients undergoing the antagonist protocol. There were no changes found in the right and left ventricular systolic or diastolic function between pituitary down-regulation and peak estradiol levels [22].

Table 2
Summary of Mean Arterial Pressure (MAP), systolic, and diastolic blood pressure changes during IVF Protocol.

Study	Protocol	Change in Blood Pressure
La Sala (1989)	GnRH agonist	From pit. downregulation to peak estradiol level, there was a significant decrease in MAP[a], SBP[b], but no significant change in DBP[c]. For women who conceived, from pit. downregulation to the luteal phase (12 days after GIFT[d]), there was a significant decrease in MAP, SBP, DBP. There were no significant changes during this time period in women who did not conceive.
Manau (1998)	GnRH agonist	No significant change in MAP from baseline (mid-follicular phase of menstrual cycle) to pituitary downregulation. Significant decrease in MAP from baseline to peak estradiol levels. There was a significant decrease in MAP from baseline 24 hours and 7 days post hCG[e] injection.
Manau (2002)	GnRH agonist	There was a significant decrease in MAP from baseline (day 7 of spontaneous menstrual cycle) to 7 days post hCG injection.
Manau (2002)	GnRH agonist	Significant increase in MAP from baseline (mid-luteal phase measurements taken from control) to pituitary downregulation (in IVF patients). Significant decrease in MAP from baseline to peak estradiol levels in IVF patient. There was a significant decrease in MAP from baseline to 11 days after hCG injection.
Nevo (2007)	GnRH agonist	No significant change in MAP from pit. downregulation to peak estradiol levels. No significant change in MAP from pit. downregulation to 8–9 days post hCG injection.
Li (2013)	GnRH agonist	Did not comment on significant changes in systolic or diastolic BP from day 5 of GnRH to peak estradiol levels. Did not comment on significant changes in systolic or diastolic BP from pit. downregulation to day 7 post-oocyte pick up or 16 after embryo transfer.
Tollan (1993)	GnRH antagonist	Significant decrease in systolic and diastolic blood pressure from baseline (day 3 of menstrual cycle) to peak estradiol levels.

|| hCG (human chorionic gonadotrophin).
[a] GnRH (gonadotrophin releasing hormone).
[b] MAP (mean arterial blood pressure).
[c] SBP (systolic blood pressure).
[d] DBP (diastolic blood pressure).
[e] GIFT (gamete intrafallopian tube transfer).

Table 3
Summary of change in cardiac function and structure over the IVF treatment protocol.

Study	Protocol	Changes observed
La Sala (1989)	GnRH agonista[a]	Pituitary downregulation to peak oestradiol levels. Significant increase in heart rate and cardiac index. Significant increase in left ventricular dimension at end diastole (LVEDD) and left ventricular dimension at end systole (LVESD).
Li (2013)	GnRH agonist	From pituitary downregulation to 7 days post-oocyte retrieval, there was an increase in left ventricular end diastolic volume and decrease in left ventricular ejection fraction. The values trended towards baseline values after this period.
Manau (2002)	GnRH agonist	Post-ovulatory day 7 before starting treatment to peak estradiol levels. Significant increase in cardiac output.
Weissman (2009)	GnRH agonist	Pituitary downregulation to peak oestradiol levels. There was a significant increase in high-frequency spectral power, and a significant decrease in the ratio of low-frequency to high-frequency spectral power. This indicates the activation of the parasympathetic arm in the modulation of heart rate variability.
Uckuyu (2010)	GnRH antagonist	Pituitary downregulation to peak estradiol levels. No significant change in right and left ventricular systolic or diastolic function.

[a] GnRH (gonadotrophin releasing hormone).

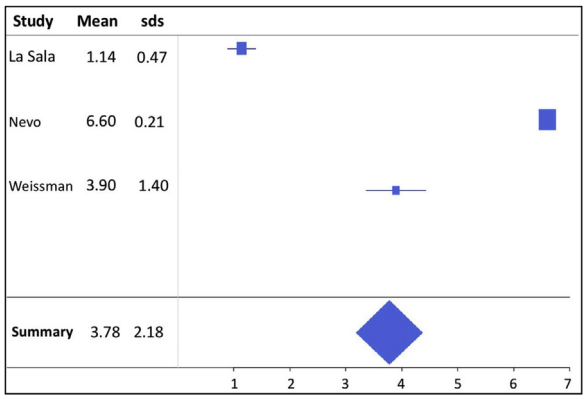

Fig. 3. Meta-analysis of 3 studies showing change in heart rate during GnRH agonist protocol from pituitary downregulation to peak estradiol levels.

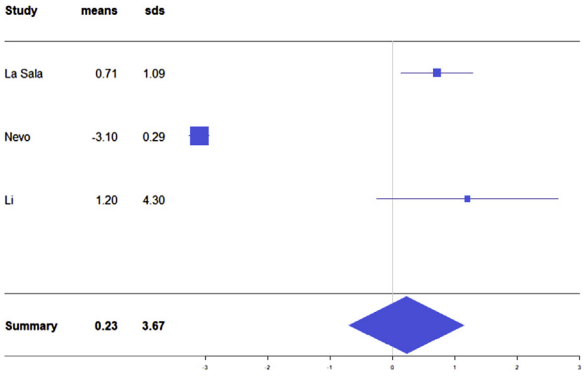

Fig. 5. Meta-analysis of 3 studies showing change in heart rate during GnRH agonist protocol from peak estradiol levels to luteal phase.

Weissman et al. reported the autonomic modulation of heart rate variability during the IVF agonist protocol. At peak estradiol levels, there was a significant decrease in the ratio of low-frequency to high-frequency spectral power, indicating parasympathetic dominance and an alteration of the balance between sympathetic and vagal control [23].

Meta-analysis

Heart rate

The meta-analysis of 3 studies undergoing the GnRH long agonist protocol showed a significant increase in heart rate of 3.78 beats per minute (bpm) (±2.18) from pituitary down-regulation to peak oestradiol levels (Fig. 3). There was also a significant increase in heart rate of 2.61 bpm (±0.95) from pituitary downregulation to the luteal phase (Fig. 4). There was no significant difference found in heart rate between peak oestradiol levels and the luteal phase (Fig. 5).

Mean arterial pressure

The meta-analysis showed a significant decrease of 2.08 mmHg (±1.79) of MAP from pituitary downregulation to the luteal phase (Fig. 6), and a significant decrease of 3.58 mmHg (±2.14) from peak serum estradiol levels to the luteal phase (Fig. 7). There was no significant difference found in MAP between pituitary down-regulation to peak estradiol levels (-0.15 mmHg [±2.08]) (Fig. 8).

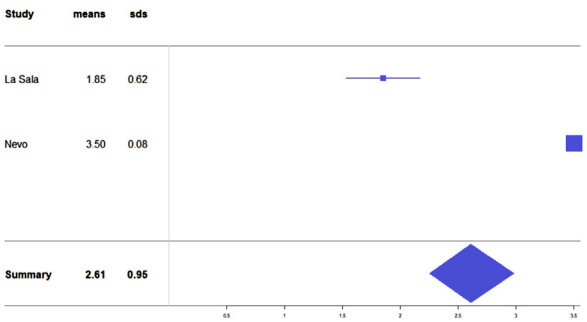

Fig. 4. Meta analysis of 2 studies showing change in heart rate during GnRH agonist protocol from pituitary down-regulation to the luteal phase.

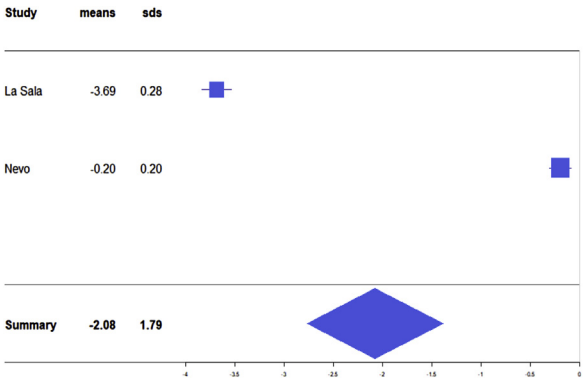

Fig. 6. Meta-analysis of 2 studies showing change in mean arterial pressure during GnRH agonist protocol from pituitary downregulation to luteal phase.

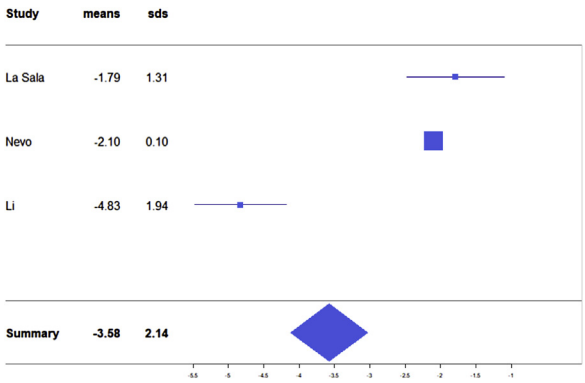

Fig. 7. Meta-analysis of 3 studies showing change in mean arterial pressure during GnRH agonist protocol from peak oestradiol level to luteal phase.

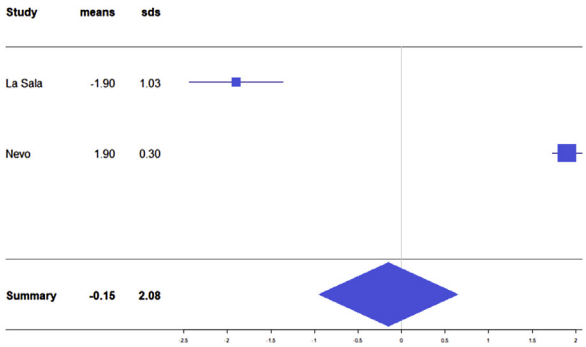

Fig. 8. Meta-analysis of 2 studies showing change in mean arterial pressure during GnRH agonist protocol from pituitary downregulation to peak oestradiol levels.

Comments

IVF treatment is associated with acute changes in maternal hemodynamic parameters. We found an increase in heart rate from pituitary down-regulation to peak oestradiol levels, not sustained through to the luteal phase. We report a significant decrease in blood pressure from baseline or pituitary down regulation to the luteal phase. Conversely, between pituitary down-regulation to peak oestradiol levels, most studies did not report a significant change in MAP, systolic, or diastolic blood pressure. Cardiac functional changes were reported for the studies on the agonist but not antagonist protocols. The importance of these findings is that profound haemodynamic perturbations occur in IVF over a very short period, usually days, at around embryonic implantation.

The role of oestrogen as a vasodilator has been reported to be mediated by oestrogen induced nitric oxide release (White, 2002). In the GnRH agonist protocol, pituitary down-regulation is initially associated with a decrease in oestradiol plasma levels. As ovarian stimulation progresses with the development of multiple follicles, oestradiol rises to supra-physiological levels, and remains elevated after hCG has been administered (Shrestha et al., 2015). Manau et al. found the changes in serum oestradiol levels in their patients to be chronologically related to changes in blood pressure, implying the inverse association between increasing oestradiol levels and blood pressure (Manau et al., 1998).

During the initial weeks of pregnancy, decrease in blood pressure is associated with homeostatic activation of the renin-angiotensin-aldosterone system (RAAS). Similarly, it is postulated that the circulatory changes to blood pressure and heart rate during IVF may also lead to the activation of the RAAS (Manau et al., 2002b). The maximum increase in plasma renin activity and aldosterone levels occurs during the luteal phase after oocyte retrieval (Manau et al., 2002a), as opposed to during ovarian stimulation when peak oestradiol levels occur. This suggests that a stimulus other than an oestrogen-related fall in blood pressure has activated the RAAS. A possible mechanism for the increase in plasma renin may be by the increased production by the ovary, shown previously by a significant increase of renin in ovarian follicular fluid after the injection of hCG (Manau et al., 2002a).

The haemodynamic changes occurring in early pregnancy could affect measurements taken in the luteal phase, which was not taken into account in all studies. One study found cardiac function to return to baseline approximately 4 weeks after the initiation of treatment, despite a continued elevation of oestradiol levels (Li et al., 2012). In contrast, another study found that in patients who became pregnant, the significant change in cardiac function was sustained through the luteal phase and did not return to baseline, whereas this was not observed in patients who did not conceive despite a continuous elevation of serum oestradiol in both cohorts (La Sala et al., 1989). Whether this is a function of oestrogen, hCG or cardiac modulation by some other mechanism is not possible to determine.

The response to stimulating hormones can vary extensively depending on the protocol and the type of ovulation maturation trigger administered. Therefore, the heterogeneity between the protocols limited the studies which could be included in the meta-analysis. The wide variation in the timing of measurement taken during the luteal phase may have further had an impact on the values.

It remains unclear as to whether the acute cardiovascular changes during IVF lead to a propensity for cardiovascular dysfunction in pregnancy. We have recently described that healthy women who develop PE and/or fetal growth restriction have higher pre-pregnancy vascular resistance, blood pressure and lower cardiac output than those with normal outcomes (Foo et al., 2018). This raises the intriguing question as to whether pre-pregnancy cardiovascular function is causatively associated with the development of hypertensive conditions and growth restriction or is itself a marker or a predisposition to adverse pregnancy outcome.

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Data statement

Additional data is available by emailing Christoph.lees@imperial.nhs.uk

Author's roles

E.F was involved in study design, execution, analysis, manuscript drafting.

R.J was involved in study design, execution, analysis, manuscript drafting and critical discussion.

L.M was involved in analysis and critical discussion.

T.S was involved in analysis, manuscript drafting and critical discussion.

C.L was involved in study design, manuscript drafting, critical discussion and overall supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Human Fertilisation & Embryology Authority. HFEA fertility treatment 2017: trends and figures. 2017.

[2] CDC US Department of Health. 2016 assisted reproductive technology national summary report. 2016.

[3] Jaspal R, Prior T, Denton J, Salim R, Banerjee J, Christoph Lees L. The impact of cross-border IVF on maternal and neonatal outcomes in multiple pregnancies: experience from a UK fetal medicine service. Eur J Obstet Gynecol Reprod Biol 2019;238:63–7, doi:http://dx.doi.org/10.1016/j.ejogrb.2019.04.030.

[4] White RE. Estrogen and vascular function. Vascul Pharmacol 2002;38:73–80, doi:http://dx.doi.org/10.1016/S0306-3623(02)00129-5.

[5] Balakrishnan K, Scott P, Oliver L. A confluence of circumstances: a case of IVF, extreme exercise and spontaneous coronary artery dissection. Int J Cardiol 2016, doi:http://dx.doi.org/10.1016/j.ijcard.2015.10.099.

[6] Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. Cochrane Database Syst Rev 2017, doi:http://dx.doi.org/10.1002/14651858.CD012103.pub2.

[7] Thomopoulos C, Salamalekis G, Kintis K, Andrianopoulou I, Michalopoulou H, Skalis G, et al. Risk of hypertensive disorders in pregnancy following assisted reproductive technology: overview and meta-analysis. J Clin Hypertens 2017;19:173–83, doi:http://dx.doi.org/10.1111/jch.12945.

[8] Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. Obstet Gynecol 2011;118:863–71, doi:http://dx.doi.org/10.1097/AOG.0b013e31822be65f.

[9] Wu Y, Chen Y, Shen M, Guo Y, Wen SW, Lanes A, et al. Adverse maternal and neonatal outcomes among singleton pregnancies in women of very advanced maternal age: a retrospective cohort study. BMC Pregnancy Childbirth 2019;19:3, doi:http://dx.doi.org/10.1186/s12884-018-2147-9.

[10] Tan S-L, Doyle P, Campbell S, Beral V, Rizk B, Brinsden P, et al. Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. Am J Obstet Gynecol 1992;167:778–84, doi:http://dx.doi.org/10.1016/S0002-9378(11)91589-0.

[11] Koivurova S, Hartikainen A-L, Karinen L, Gissler M, Hemminki E, Martikainen H, et al. The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990-1995. Hum Reprod 2002;17:2897–903, doi:http://dx.doi.org/10.1093/humrep/17.11.2897.

[12] Dayan N, Filion KB, Okano M, Kilmartin C, Reinblatt S, Landry T, et al. Cardiovascular risk following fertility therapy: systematic review and meta-analysis. J Am Coll Cardiol 2017, doi:http://dx.doi.org/10.1016/j.jacc.2017.07.753.

[13] Liberati A. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:, doi:http://dx.doi.org/10.7326/0003-4819-151-4-200908180-00136 W.

[14] Cochrane handbook for systematic reviews of interventions version 5.1.0. In: Higgins JPTGS, editor. 2011. . (accessed March 18, 2019) www.handbook.cochrane.org.

[15] La Sala GB, Gaddi O, Bruno G, Brandi L, Cantarelli M, Salvatore V, et al. Noninvasive evaluation of cardiovascular hemodynamics during multiple follicular stimulation, late luteal phase and early pregnancy. Fertil Steril 1989;51:796–802, doi:http://dx.doi.org/10.1016/S0015-0282(16)60669-6.

[16] Nevo O, Soustiel JF, Thaler I. Cerebral blood flow is increased during controlled ovarian stimulation. Am J Physiol Hear Circ Physiol 2007;293, doi:http://dx.doi.org/10.1152/ajpheart.00633.2007.

[17] Li Y, Sun X, Zang L, Zhang Q, Li J, Zou S. Correlation between steroid hormonal levels and cardiac function in women during controlled ovarian hyperstimulation. Endocrine 2013;44:784–9, doi:http://dx.doi.org/10.1007/s12020-013-9953-7.

[18] Manau D, Balasch J, Arroyo V, Jiménez W, Fabregues F, Casamitjana R, et al. Circulatory dysfunction in asymptomatic in vitro fertilization patients. Relationship with hyperestrogenemia and activity of endogenous vasodilators. J Clin Endocrinol Metab 1998;83:1489–93, doi:http://dx.doi.org/10.1210/jc.83.5.1489.

[19] Manau D, Arroyo V, Jiménez W, Fábregues F, Vanrell JA, Balasch J, et al. Chronology of hemodynamic changes in asymptomatic in vitro fertilization patients and relationship with ovarian steroids and cytokines. Fertil Steril 2002;77:1178–83, doi:http://dx.doi.org/10.1016/S0015-0282(02)03116-3.

[20] Tollan A, Øian P, Kjeldsen SE, Holst N, Eide I. Effects of ovarian stimulation on blood pressure and plasma catecholamine levels. Scand J Clin Lab Invest 1993;53:353–8, doi:http://dx.doi.org/10.3109/00365519309086627.

[21] Manau D, Fábregues F, Arroyo V, Jiménez W, Vanrell JA, Balasch J. Hemodynamic changes induced by urinary human chorionic gonadotropin and recombinant luteinizing hormone used for inducing final follicular maturation and luteinization. Fertil Steril 2002;78:1261–7, doi:http://dx.doi.org/10.1016/S0015-0282(02)04394-7.

[22] Uckuyu A, Ciftci CF, Ozcimen EE, Ciftci O, Toprak E, Turhan E. Effect of controlled ovarian hyperstimulation treatment on cardiac function. J Reprod Med 2010;55:503–8.

[23] Weissman A, Lowenstein L, Tal J, Ohel G, Calderon I, Lightman A. Modulation of heart rate variability by estrogen in young women undergoing induction of ovulation. Eur J Appl Physiol 2009;105:381–6, doi:http://dx.doi.org/10.1007/s00421-008-0914-4.