Controlled ovarian stimulation leads to cardiovascular changes in patients undergoing in vitro fertilization

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ABSTRACT

Objective: To study hemodynamic changes along controlled ovarian stimulation in women undergoing in vitro fertilization.
Study design: Prospective observational cohort study conducted at Mother and Child Department of University Hospital Federico II, in Naples, Italy, between April 2021 and July 2022. Sixty-eight infertile patients undergoing controlled ovarian stimulation with gonadotropin, antagonist protocol and a fresh embryo transfer were included. Haemodynamic assessment was carried out using UltraSonic Cardiac Output Monitor at baseline (T1), estradiol peak (T2), fresh embryo-transfer day (T3). To evaluate relationships between quantitative variables and groups a Student T test for independent data was assessed. One-way analysis of variance (ANOVA) was used to determine the differences between the means of three time points (T1, T2 and T3) for quantitative variables. A mixed-model analysis of variance (ANOVA) was used to determine the differences between groups, among time points (T1, T2 and T3).
Results: Sixty-eight patients were included. Significant differences over the three time points have been observed for CO (f = 3.78 l/min; p = 0.025), SVI (f = 3.56 ml/m^2;p = 0.013), and RSVI (f = 4.84 dscm-5 m^2; p = 0.009). No significant differences in trends have been found between beta hCG positive and beta hCG negative groups. There were no significant differences in maternal hemodynamic parameters at time-point T3 between patients treated with hCG 10,000 UI and with Triptorelin. Patients considered at increased risk of hyperstimulation reported a significant increase in SVI at baseline (26.9 ± 9.0 mL/m^2 vs 21.9 ± 7.0 mL/m^2; p = 0.010).
Conclusion: According to the results of our study, during controlled ovarian stimulation with antagonist protocol, patients undergo significant changes in maternal cardiovascular parameters over a very short period.

Introduction

Sex-steroid hormones have an influence on the cardiovascular system. Estrogen induces vascular muscle cell relaxation, enhancing the production of vasodilatory mediators and increasing the expression of beta-adrenergic receptors [1–3]. Moreover, it has an anti-apoptotic effect in cardiomyocytes, even if the underlying mechanism is largely unknown [2]. It has been reported that administration of estradiol after

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Abbreviations: CO, cardiac output; SV, stroke volume; HR, heart rate; PV, plasma volume; SVR, systemic vascular resistance; MAP, mean arterial pressure; COS, controlled ovarian stimulation; Gn, gonadotropin; SVI, stroke volume index; SVRI, systemic vascular resistance index; CI, cardiac index.

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hemorrhagic shock improves Cardiac Output (CO), Stroke Volume (SV), and Mean Arterial Pressure (MAP) [4]. Cardiovascular effects of progesterone are less defined. It seems to modulate vascular tone increasing prostacyclin synthesis and regulating calcium channel activity [1,2]. Moreover, a direct role of progesterone in response to vascular injury has been postulated [5]. Estrogen and progesterone also affect renin-angiotensin system, modulating body fluids [1].

Even if evidence is very limited [1,6–9], it seems that hormonal fluctuations during the natural menstrual cycle have a poor impact on cardiovascular system. On the contrary, the consistent increase of sex hormones during pregnancy leads to expanding blood volume and significant hemodynamic changes [1]. Maternal cardiovascular adaptation to healthy pregnancy is characterized by increased CO, SV and Heart Rate (HR), as a consequence of increased Plasma Volume (PV) and preload, and decreased Systemic Vascular Resistance (SVR) and MAP [10]. Early abnormal cardiovascular adaptation to the pregnancy has been related to increased risk of adverse outcomes, such as Hypertensive Disorders of Pregnancy (HDP), Fetal Growth Restriction (FGR) [11–16] and complicated labour [17–20].

Singleton pregnancies from In Vitro Fertilization (IVF) have been associated to increased risk of adverse maternal and perinatal outcome [21–25], and, above all, increased risk of HDP [25].

However, it is still not clear whether the underlying cause is the Controlled Ovarian Stimulation (COS), the IVF itself, the underlying infertility or pre-existing risk factors, such as an increased maternal age [26,27].

In singleton IVF pregnancies, abnormal cardiovascular adaptation during the third trimester of pregnancy, characterized by low CO and high SVR, has been described, and it has been postulated as a possible cause of adverse pregnancy outcome [28].

However, little is known about the cardiovascular response to COS before embryo transfer and if this stimulation has any effect on cardiovascular adaptation to implantation and pregnancy. A recent systematic review and *meta*-analysis of nine studies [27] reported that IVF leads to acute hemodynamic changes during COS. However, most of the evidence is related to changes in HR [17–19] and MAP [18,19,29–32]. Few studies described changes in cardiac function over COS, reporting an increase in CO at estradiol peak [29] and an increase in left ventricular dimension at the end of both diastole and systole [19,30]. However, scientific evidence so far is very limited, especially in case of Gonadotropin-Relaesing Hormone (GnRh) antagonist protocol [33].

The aim of this monocentric prospective observational study was to evaluate hemodynamic changes along COS protocol in women undergoing IVF.

Methods

Study design, setting and population

This was a prospective observational cohort study conducted at Mother and Child Department of University Hospital Federico II, in Naples, Italy, between April 2021 and July 2022.

Patients undergoing COS with Gn and antagonist protocol, and a fresh embryo transfer were included.

Ovarian stimulation with Gn was initiated on day 2 or 3 of the menstrual cycle. After 3 or 4 days from the start of the ovarian stimulation, Gn dose was adjusted according to the patient's response, based on transvaginal ultrasound examination and serum levels of estradiol and progesterone. When the follicle size was ≥12 mm, the GnRH antagonist was given at 0,25 mg/day until the trigger day. Ovulation was triggered by human Chorionic Gonadotropin (hCG) 10,000 UI or with Triptorelin 0,2 mg, when the mean diameter of two dominant follicles increased to 18 mm or more, or when the mean diameter of three dominant follicles increased to 17 mm. Thirty-six to 38 h after the trigger event, an expert in IVF retrieved the oocytes. The embryo was cultured until day 3 or day 5 and then was transferred. Patients considered at increased risk of ovarian hyoerstimulation, according to Lainas et al. [34], were rescheduled for frozen embryo transfer.

The exclusion criteria were frozen embryo transfer, heterologous fertilization, unknown beta hCG after embryo transfer. Considering the exploratory nature of this study, a convenience sample of patients, satisfying eligible criteria, was recruited.

Ethical approval

This study has been approved by The Ethical Local Committee. A written consent form has been obtained from all included participants.

Research investigations

At participant enrollment, anamnestic, clinical, demographic, and biochemical data were recorded on a dedicated database.

Blood Pressure (BP) was measured using an automatic device (Omron M7, OMRON Healthcare Europe BV, Hoofddorp, The Netherlands), after a 5-minute period of physical inactivity.

Haemodynamic assessment was carried out by a single trained operator using UltraSonic Cardiac Output Monitor (USCOM ®, USCOM Ltd., Coffs Harbour, Asutralia). To reduce intra-observer variability, all measurements were recorded under standardized conditions, with participants lying in a semi-recubent position. USCOM probe was positioned in the suprasternal space to obtain a minimum of three consecutive Doppler waves, as previously described [13,35,36].

The following hemodynamic parameters have been recorded: HR, CO, Cardiac Index (CI), SV, Stroke Volume Index (SVI), SVR, Systemic Vascular Resistance Index (SVRI).

USCOM measurements were recorded at three different time points: T1, baseline (first day of menstrual cycle before the beginning of COS); T2, estradiol peak (day of hCG or Triptorelin administration); and T3, fresh embryo transfer day. Patients have been assessed at similar times (between 12 pm and 2 pm), in order to avoid possible circadian effects on hemodynamic changes.

Beta hCG levels two weeks after embryo transfer were also recorded.

Statistical analysis

Descriptive analysis was carried out using mean ± standard deviation for quantitative variables, while frequencies and percentages were used to describe the categorical variables. Normality distribution was tested by the Shapiro-Wilk test. To evaluate relationships between quantitative variables and groups a Student T test for independent data was assessed.

One-way analysis of variance (ANOVA) was used to determine the differences between the means of three time points (T1, T2 and T3) for quantitative variables. Homogeneity of variances was evaluated using Bartlett test. For significant trends, this analysis was followed by Bonferroni correction for multiple comparisons. A mixed-model analysis of variance (ANOVA) was used to determine the differences between beta hCG groups, among time points (T1, T2 and T3), and their interaction. Homogeneity of variance between groups along the time points was verified using the Levene test. The Huynh-Feldt epsilon was applied to verify the assumption of sphericity, otherwise the Greenhouse correction was used. A statistical significance was set at the level of ≤0.05, unless adjustment for multiple comparisons was needed. All analyses were performed using Stata software v17 (StataCorp, College Station, USA).

Results

Eighty-five patients gave their consent to participate in the study and were prospectively followed up from T1 to T3. Out of 85 women, 17 (20 %) women were excluded, due to an increased risk of ovarian hyperstimulation, and rescheduled for frozen embryo transfer.

None of the included patients experienced failed egg retrieval or failed fertilization.

Clinical, anamnestic, and demographic data of the 68 included patients are reported in Table 1.

Maternal hemodynamic parameters

Maternal hemodynamic parameters over the three different time-points are reported in Table 2.

No correlation has been found between maternal age and each hemodynamic parameter at T1.

The One-way ANOVA analysis indicated statistically significant differences for CO (f = 3.78 l/min; p = 0.025), SVI (f = 3.56 ml/m^2;p = 0.013), and SVRI (f = 4.84 dscm^{-5}m^2; p = 0.009).

After Bonferroni post-hoc analysis, CO and SVI at estradiol peak (T2) were significantly higher compared to baseline (T1) (CO 3.4 ± 1.6 l/min vs 3.0 ± 1.0 l/min, p = 0.020; SVI 24.8 ± 8.9 ml/m^2 vs 21.9 ± 7.0 ml/m^2, p = 0.030), while SVRI was significantly decreased (4204.2 ± 1521.6 dscm^{-5}m^2 vs 4879.8 ± 1919.5 dscm^{-5}m^2, p = 0.007). Fig. 1 represents graphical trends of CO, SVI and SVRI over three time-points.

Maternal hemodynamic parameters and pregnancy test results

Out of 68 patients, 16 (23.5 %) had positive beta hCG two weeks after embryo transfer.

The ANOVA mixed-model analysis did not show a statistically significant effect of the time, of beta hCG groups and of the interaction between the time points and beta hCG groups (Table 3).

Effect of different medications for controlled ovarian stimulation on maternal hemodynamics

Among 68 patients, 38 (55.9 %) were induced using recombinant FSH (rFSH), 26 (38.2 %) using Human Menopausal Gonadotropin (hMG), and 4 (5.9 %) using α corifolitropin, alone or with the addition of gonadotropins (hMG or rFSH).

The ANOVA mixed-model analysis did not show a statistically significant effect of the time, of the type of drug, and of the interaction between the time points and drugs groups (Table 4).

Effect of trigger treatment on maternal hemodynamics

Trigger treatments were available for 67 out of 68 patients. There were no significant differences in maternal hemodynamic parameters at time-point T3 between patients treated with beta hCG 10,000 UI (46 patients, 67.7 %) and with Triptorelin (22 patients, 33.3 %) used at estradiol peak to trigger the ovulation (Table 5).

Table 1
Clinical, anamnestic, and demographic data of the sample.

Variables	N = 68
Age (years)	35.9 ± 4.4
Weight (kilograms)	66.2 ± 12.5
Height (meters)	1.60 ± 0.1
Body Mass Index (kg/m^2)	25.0 ± 4.8
Caucasian	68 (100 %)
Smoking	17 (25.0 %)
Primary infertility	52 (76.5 %)
Causes of infertility	
Male	26 (38.2 %)
Female	27 (39.7 %)
Idiopatic	15 (22.1 %)
Retrieved oocytes	6.1 ± 3.4
Anti-mullerian hormone (AMH) (ng/ml)	2.6 ± 4.3
Luteinizing Hormone (LH) (mUI/ml)	7.3 ± 7.9
Follicle Stimulating Hormone (FSH) (mUI/ml)	8.7 ± 3.8
Estradiol (E2) (pg/ml)	48.5 ± 31.2

Data are presented as N (%) or means ± standard deviations when appropriate.

Table 2
Anova analysis for maternal hemodynamic parameters at three different times-points (T1, baseline – first day of menstrual cycle; T2, estradiol peak; and T3, embryo transfer).

	T1	T2	T3	*f, p-value*§
SV (ml/m^2)	38.0 ± 12.3	42.9 ± 16.0	39.7 ± 14.7	**2.96, p = 0.060**
SVI (ml/m^2)	21.9 ± 7.0	24.8 ± 8.9*	22.8 ± 7.8	**3.56, p = 0.013**
HR (bpm)	80.5 ± 21.6	82.6 ± 22.5	83.0 ± 20.8	0.73, p = 0.485
CO (l/min)	3.0 ± 1.0	3.4 ± 1.6**	3.1 ± 1.2	**3.78, p = 0.025**
CI (ml/m^2)	1.7 ± 0.6	2.0 ± 0.9	2.0 ± 1.9	1.44, p = 0.241
SVR (dscm^{-5})	2781.4 ± 1092.5	2516.3 ± 1022.2	2723.9 ± 1114.4	2.03, p = 0.135
SVRI (dscm^{-5}m^2)	4879.8 ± 1919.5	4204.2 ± 1521.6***	4614.2 ± 1769.0	**4.84, p = 0.009**

Data are presented as means ± standard deviations.
§f and p-values are for ANOVA analysis, Bonferroni Post-hoc analysis: * T2 vs T1: *p = 0.030*; ** T2 vs T1: *p = 0.022*; *** T2 vs T1: *p = 0.007*.

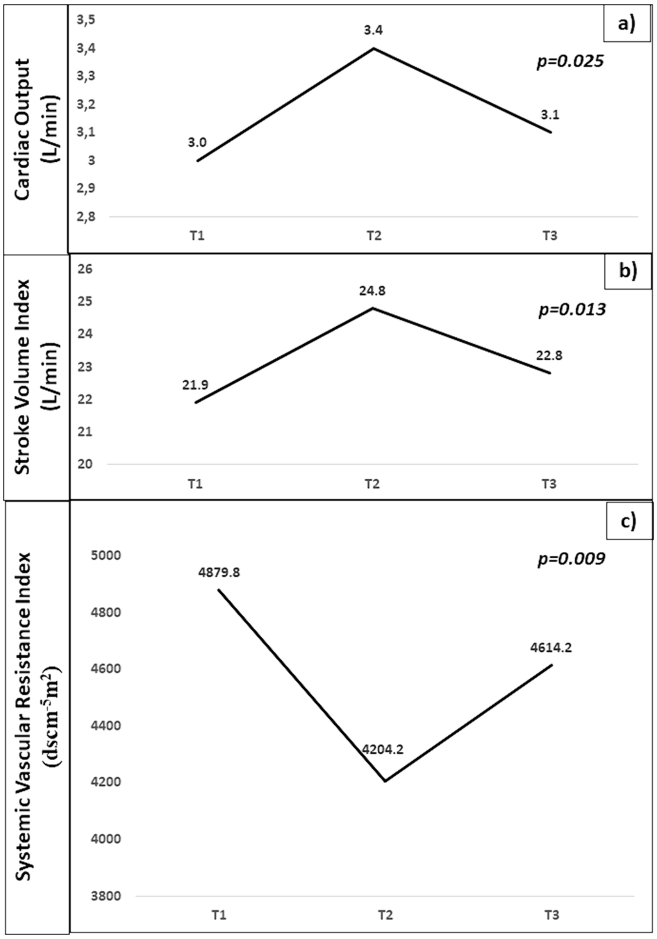

Fig. 1. ANOVA analysis for the comparison of Cardiac Output (CO), Stroke Volume Index (SVI) and Systemic Vascular Resistance Index (SVRI) in the three time points. *Bonferroni Post-hoc analysis: a) T2 vs T1: p = 0.022; b) T2 vs T1: p = 0.030; c) T2 vs T1: p = 0.007.

Maternal hemodynamic parameters in fresh and frozen embryo transfer

Seventeen patients (20 %) were excluded from the analysis because

Table 3
Anova mixed model for maternal hemodynamic parameters in relation to time-points and Beta hCG group.

Variability source	*f*	*df*	*p-value**
SV (ml/m^2)			
Time	1.30	2,123	0.275
Group beta hCG	0.03	1,123	0.874
Interaction (time- group beta hCG)	0.48	2,123	0.618
SVI (ml/m^2)			
Time	1.70	2,123	0.187
Group beta hCG	0.56	1,123	0.458
Interaction (time- group beta hCG)	0.45	2,123	0.639
HR (bpm)			
Time	0.12	2,123	0.887
Group beta hCG	1.38	1,123	0.243
Interaction (time- group beta hCG)	0.54	2,123	0.587
CO (l/min)			
Time	2.11	2,123	0.125
Group beta hCG	0.88	1,123	0.351
Interaction (time- group beta hCG)	0.23	2,123	0.791
CI, (l/min/m^2)			
Time	2.87	2,123	0.060
Group beta hCG	0.30	1,123	0.583
Interaction (time- group beta hCG)	2.84	2,123	0.060
SVR			
Time	1.11	2,123	0.331
Group beta hCG	0.16	1,123	0.694
Interaction (time- group beta hCG)	0.12	2,123	0.886
SVRI (dscm^{-5}m^2)			
Time	2.56	2,123	0.081
Group beta hCG	0.55	1,123	0.459
Interaction (time- group beta hCG)	0.38	2,123	0.683

*f,df and p-values for Anova mixed model with Huynh-Feldt epsilon.

Table 4
Anova mixed model for maternal hemodynamic parameters in relation to time-points and drugs used for ovarian stimulation.

Variability source	*f*	*df*	*p-value**
SV (ml/m^2)			
Time	0.76	2,121	0.470
Drugs	0.78	2,121	0.461
Interaction (time- drugs)	2.03	4,121	0.094
SVI (ml/m^2)			
Time	0.93	2,121	0.396
Drugs	1.06	2,121	0.352
Interaction (time- drugs)	2.32	4,121	0.061
HR (bpm)			
Time	1.47	2,121	0.232
Drugs	0.97	2,121	0.383
Interaction (time- drugs)	1.72	4,121	0.149
CO (l/min)			
Time	1.99	2,121	0.918
Drugs	0.09	2,121	0.140
Interaction (time- drugs)	0.87	4,121	0.485
CI, (l/min/m^2)			
Time	0.36	2,121	0.604
Drugs	0.51	2,121	0.695
Interaction (time- drugs)	0.29	4,121	0.886
SVR			
Time	0.53	2,121	0.630
Drugs	0.46	2,121	0.592
Interaction (time- drugs)	0.23	4,121	0.919
SVRI (dscm^{-5}m^2)			
Time	0.93	2,121	0.396
Drugs	0.92	2,121	0.404
Interaction (time- drugs)	0.27	4,121	0.898

*f,df and p-values for Anova mixed model with Huynh-Feldt epsilon.

they were considered at increased risk of ovarian hyperstimulation and rescheduled for a frozen embryo transfer.

Comparing these patients with those undergoing fresh embryo transfer, we found a significantly higher SVI at baseline (T1) (26.9 ± 9.0 mL/m^2 vs 21.9 ± 7.0 mL/m^2; $p = 0.010$). No significant differences were observed for all the other parameters.

Discussion

Summary of study findings

In our monocentric prospective observational cohort study, we found significant maternal cardiovascular changes along COS antagonist protocol in women undergoing IVF and fresh embryo transfer. In particular, CO and SVI significantly increased, while SVRI significantly decreased at estradiol peak compared to baseline. There were no significant differences in hemodynamic profile from pre-conceptional period to after the embryo transfer between patients achieving a positive beta-hCG and those who did not. Moreover, different trigger treatments (Triptorelin or hCG), and different medications for ovulation induction seemed not to affect maternal hemodynamic changes. A significantly higher SVI at baseline was observed in patients considered at increased risk of ovarian hyperstimulation and rescheduled for a frozen embryo transfer.

Interpretation of study findings and comparison with the literature

According to the results of our study, during COS with antagonist protocol patients undergo significant changes in maternal cardiovascular parameters over a very short period. These changes are expressed mainly at estradiol peak and could be related to the vasoactive effect of estrogens [27], that have been demonstrated in animal models and, recently, in humans. In ovariectomized sheep, acute administration of estradiol was associated with increased CO and arterial flow velocity, and decreased SVR [37]. In human studies of forearm endothelium dependent vasodilation, estrogen improved relaxation in post-menopausal women [6,38,39].

Table 5
Maternal hemodynamic parameters at T3 (embryo transfer) in patients stratified by trigger treatments (hCG vs Triptorelin).

	hCG (n = 45)	Triptorelin (n = 22)	*p-value*§
SV (ml/m^2)	39.6 ± 14.6	38.7 ± 14.8	0.821
SVI (ml/m^2)	22.8 ± 7.8	22.3 ± 7.9	0.820
HR (bpm)	83.3 ± 23.1	82.1 ± 16.1	0.825
CO (L/min)	3.1 ± 1.2	3.1 ± 1.2	0.807
CI (ml/m^2)	2.1 ± 2.3	1.8 ± 0.7	0.588
SVR (dscm^{-5})	2770.0 ± 1063.9	2682.2 ± 1240.9	0.773
SVRI (dscm^{-5}m^2)	4683.8 ± 1712.8	4541.4 ± 1936.8	0.769

Data are presented as means± standard deviations.
§p-values are for Student T test for independent data.

Previous studies reported cardiovascular changes along agonist protocol [17,19,29,30]; in particular, La Sala et al. [19] and Manau et al. [29] reported an increase in CO and CI at estradiol peak. On the contrary, the only available study on the effect of antagonist protocol on maternal cardiovascular profile reported no changes along the protocol

[33]. The authors performed a transthoracic echocardiographic examination in twenty-one patients at the beginning of follicular phase and after the administration of the trigger therapy, reporting no changes in cardiac function. It should be acknowledged, however, that the sample size was relatively small.

Galanti et al. [40] compared the maternal hemodynamic profile of 11 women with a positive pregnancy test to that of 34 women with negative pregnancy test after IVF, reporting significantly higher SVR at mid-luteal phase and at embryo transfer in women with negative pregnancy test. According to these results, the authors hypothesized that embryo implantation might be positively influenced by a favorable maternal hemodynamic profile. In contrast with this study, when we compared women with positive Beta hCG test to those with negative test we could not find any difference along the three considered time-points. A possible explanation of a such discrepancy might be related to the fact that Galanti et al. included patients undergoing both fresh and frozen embryo transfer, while we excluded frozen embryo transfers. Indeed, our aim was to compare only patients undergoing COS stimulation just before embryo transfer. Moreover, it is undeniable that embryo implantation is a very complex mechanism involving several factors and hemodynamic adaptation could be just a contributor of a more intricate process.

Further studies with a larger sample size are needed to clarify the effect of pre-conceptional maternal hemodynamic profile on implantation in IVF conceptions.

Strengths and limitations of the study

This study offers a valuable contribution to current literature, considering the paucity of data on this topic. To the best of our knowledge, this is the largest study addressing maternal hemodynamic changes along antagonist protocol. We prospectively followed a cohort of women with standardized protocol and by means of non-invasive maternal hemodynamic assessment.

The main limitation of this study is related to its small sample size, precluding the possibility of subgroup analysis (e.g. stratification by causes of sterility or other sub-group analysis). However, previously published studies on this topic are also relatively small. Moreover, we did not report on hemodynamic changes during the mid-luteal phase, representing a fundamental moment for the implantation; to not further stress these patients, undergoing a considerable number of outpatient visits, we combined the USCOM assessments with the scheduled examinations, leading to the lack of data during the mid-luteal phase. Considering that data on hemodynamic changes during physiological menstrual cycle are very limited and controversial [1,6–9], comparing our results to hemodynamic changes in a group of physiological women not undergoing stimulation, would have enforced our results. Finally, a lack of long-term outcome in patients achieving conception after COS does not allow speculations on the possible role of acute maternal hemodynamic changes on pregnancy complications.

Clinical and research implication

IVF pregnancies have been reported to be at higher risk of maternal complications. Acute changes in maternal cardiovascular function in a such short period during COS stimulation may contribute to the development of pregnancy adverse outcome. These preliminary data are insufficient to draw recommendations on cardiac assessment in IVF patients. Considering that COS has an impact on hemodynamics, with short term variations that, according to the literature [1], it hasn’t been observed in normal menstrual cycle, our findings lead the way to further researches, to identify if there is a hemodynamic response more favorable to the implantation and to positive pregnancy outcomes, or if some parameters can help in prediction of patients’ response to stimulation. In our study, we observed that patients at increased risk of hyperstimulation had higher SVI. If this result is confirmed by larger studies, it could explain some cases of hyperstimulation occurring in women without known risk factors and identify a subgroup of IVF patients that could benefit from a freeze all protocol. However, further research on this topic is needed to clarify a possible underlying mechanism and risk factors.

Conclusion

According to our results, women undergo acute changes in CO, SVI and SVRI during COS.

We did not identify significant differences in hemodynamic response to COS after stratification by pregnancy test results. However, we think that further studies on this topic could identify hemodynamic parameters that could be useful as predictors of good response to COS and successful implantation.

CRediT authorship contribution statement

Laura Sarno: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ida Strina:** Writing – review & editing, Supervision, Investigation, Data curation. **Paola Borrelli:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Michela Palese:** Writing – review & editing, Data curation. **Antonio Angelino:** Writing – review & editing, Data curation. **Vincenzo Marrone:** Data curation. **Antonietta Perrone:** Software, Methodology, Data curation. **Giuseppe Maria Maruotti:** Writing – review & editing. **Tamara Stampalija:** Writing – review & editing. **Maurizio Guida:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization.

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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