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Association between fertility treatments and early placentation markers

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ABSTRACT

Introduction: Pregnancies resulting from fertility treatments are at higher risk of placenta-mediated complications. Hence, we aimed to estimate the association between fertility treatment and levels of first-trimester markers of placentation.

Methods: We conducted a cohort study in an academic center from 03/2011 to 12/2014. Adult nulliparous women with singleton pregnancies were recruited between 11^{+0} and 13^{+6} weeks of gestation. Data on maternal characteristics, medical history, and pregnancies conceived through fertility treatments (whether ovulation agents, insemination or assisted reproductive technologies) were collected. Maternal serum concentrations of PlGF, sFlt-1, PAPP-A, AFP, and free β-hCG were obtained, and notches and UtA-PI were measured using Doppler ultrasound. Mean Multiple of the Medians (MoM) and frequencies were computed to estimate the mean differences (MD) or risk ratios (RR) comparing fertility treatment to spontaneous pregnancies.

Results: 427 (9%) pregnancies out of 4815 were conceived through fertility treatments, using ovulation agents (n = 233, 5%), insemination (n = 174, 4%) and/or assisted reproductive technologies (n = 85, 2%). The latter were associated with significantly lower $\log_{10}$PAPP-A MoM (adjusted MD: −0.02, 95%CI: −0.04 to −0.01), lower $\log_{10}$PlGF MoM (adjusted MD: −0.04, 95%CI: −0.06 to −0.01) and higher $\log_{10}$free β-hCG MoM (adjusted MD: 0.05, 95%CI: 0.01 to 0.09) compared to spontaneous pregnancies. Ovulation agents and insemination were associated with the presence of notches (adjusted RR: 1.24, 95%CI: 1.14 to 1.35; and 1.27, 95%CI: 1.15 to 1.42, respectively) and higher $\log_{10}$UtA-PI MoM (adjusted MD: 0.16, 95%CI: 0.08 to 0.24; and 0.17, 95%CI: 0.07 to 0.27, respectively) than spontaneous pregnancies.

Conclusion: Fertility treatments are associated with significant variations in markers of placentation.

1. Introduction

Infertility is a common disorder affecting approximately 16% of Canadian couples [1]. In industrialized countries, there has been an increase in demands for medical assistance to conceive over the last decades [2]. Pregnancies that have been conceived through assisted reproductive technologies (ART), using either conventional in vitro fecundation (IVF) or intracytoplasmic sperm injection (ICSI), are associated with higher risks of placenta-mediated complications of pregnancy, including preeclampsia, intrauterine growth restriction, preterm delivery and pregnancy loss [3,4], while those following ovulation agents and insemination have been scarcely studied. Some authors have suggested a relation between fertility treatments and placental function as well as early fetal development [5,6].

There is a growing interest in studying the relation between the mode of conception, placentation and fetal development [3,5–8]. Previous studies reported differences in early expression of plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) in women who conceive through ART compared to those who conceived spontaneously [9]. Furthermore, other maternal serum biomarkers such as placental growth factor (PlGF), PAPP-A, soluble fms-like tyrosine kinase-1 (sFlt-1), and uterine artery doppler have shown promising discriminative capacities in the prediction of early preeclampsia, a complication of pregnancy associated with placental dysfunction [10–13]. Hence, we aimed to estimate the variations in the levels of various first-trimester biomarkers of placental function following fertility treatments compared to spontaneous pregnancies.

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2. Materials and methods

This study is a secondary analysis using data from a large prospective cohort study of great obstetrical syndromes (GOS study) conducted between March 2011 and December 2014 in two sites of an academic center (CHU de Québec – Université Laval, sites CHUL and HSFA) in Quebec City [14]. The ethics committee of the CHU de Québec – Université Laval approved the study (CS10-09-085, 2012–629). All women signed an informed consent.

The academic center is the only hospital facility designated for perinatal health care in the region. Women were recruited in the cohort through family doctors and obstetricians at their initial visit and were instructed to contact the research team for an appointment between 11^{+0} and 13^{+6} weeks of gestation if they agreed to participate.

Adult nulliparous women with living singleton foetus were eligible. We excluded multiple gestations, congenital anomalies or suspicion of chromosome abnormalities leading to medical abortion.

During the initial study visit between 11^{+0} and 13^{+6} weeks, a trained nurse measured the weight and height of participants. The BMI was computed using those measurements. We collected information on maternal ethnicity, smoking habits, chronic diseases (e.g., pre-existing hypertension, diabetes) and obstetrical history. Fertility treatment are provided in one of the 2 sites (CHUL) of our study center, where infertility investigations take place after a minimum of one year of unsuccessful attempts to get pregnant. Information on the use of fertility treatment for the conception of the current pregnancy was collected using a questionnaire with the following options: ovulation agents, artificial insemination and ART (IVF or ICSI). Insemination and ART were considered mutually exclusive. Hence, women who had indicated using insemination and ART were considered in the ART group only. Ovulation agents could be combined with other treatments. Women could also specify other types of fertility treatment or add precisions in the form. Sperm donation, and metformin being the most frequently reported in the open-ended question on other fertility treatment, we also considered those 2 types of treatments in exploratory analyses. During their initial visit, all women underwent an ultrasound examination by a sonographer with Fetal Medicine Foundation (FMF) certification using a Voluson E8 (GE Healthcare). Crown rump length was measured to estimate the gestational age using Hadlock curve [15]. Doppler measurement of uterine artery pulsatility index (UtA-PI) and notching (present or absent) were also obtained. Maternal serum samples of approximately 10 mL were drawn during this initial visit by a research nurse. Samples were centrifuged, aliquoted and stored at −80 °C until biomarkers measurements were conducted. Biomarkers concentrations were measured after the end of recruitment by a technician blinded to the clinical data. PlGF, sFlt-1, PAPP-A, alpha-fetoprotein (AFP) and free beta human chorionic gonadotropin (β-hCG) were measured by immunofluorescence using B·R·A·H·M·S KRYPTOR (Thermo Scientific B·R·A·H·M·S, Hennigsdorf, Germany). Undetectable concentrations were considered as half the minimal detection level. When appropriate, the values of biomarkers were log-transformed to achieve a gaussian distribution and were converted to multiple of the median (MoM) adjusted for gestational age at measurement, based on ultrasound estimation of crown rump length.

2.1. Statistical analyses

We computed differences between spontaneous pregnancies and pregnancies following fertility treatments (ovulation agents, insemination and ART) in $\log_{10}$ PlGF MoMs, $\log_{10}$ sFlt-1 MoMs, $\log_{10}$ PAPP-A MoMs, $\log_{10}$ AFP MoMs, $\log_{10}$ free β-hCG MoMs and $\log_{10}$ UtA-PI MoMs, with their 95% confidence intervals (CI). The deviations of mean differences from the null were tested using a *t*-test. The biomarkers' mean MoMs of treatment subtypes were contrasted against the mean MoMs of women with spontaneous pregnancies. We constructed generalized linear models to evaluate the association between treatments (any or each specific subtypes) and $\log_{10}$ PlGF MoMs, $\log_{10}$ sFlt-1 MoMs, $\log_{10}$ PAPP-A MoMs, $\log_{10}$ AFP MoMs, $\log_{10}$ free β-hCG MoMs and $\log_{10}$ UtA-PI MoMs individually, while adjusting for maternal characteristics (maternal age, BMI, ethnicity, smoking, pre-existing diabetes and hypertension). Presence of notching was compared using fisher exact tests or adjusted generalized linear models with binomial distribution and log link. In sensitivity analyses, generalized additive models were built using splines terms for maternal age and BMI. We conducted additional analyses exploring the subcategory of women who reported a sperm donation, and also those who reported using metformin as a fertility treatment.

In case more than 10% of data would be missing, we planned on using multiple imputations if deemed appropriate. In all analyses, the "non-exposed" group was restricted to women with spontaneous pregnancies. A two-sides type-I error lower than 5% was considered significant. All analyses were conducted using SAS statistical software packages (Version 9.4, SAS Institute Inc. Cary, NC, USA).

3. Results

Among 5005 women screened for eligibility, 4815 were eligible to our study (Table 1). Fertility treatments were reported in 409 pregnancies (8.5%). Use of fertility treatments other than those initially considered in our study was reported in 18 pregnancies (0.4%).

Ovulation stimulation or induction was the most frequently used method (n = 233; 4.8%), followed by insemination (n = 174; 3.6%) and ART (n = 85; 1.8%). A combination of ovulation agents and insemination was reported by 79 women (1.6%) and ovulation agents with ART by 4 women (0.1%). In addition, 43 women (0.9%) reported sperm donation, 14 (32.6%) of which had ovulation agents and 4 (9.3%) had ART. Women with fertility treatments were older, had higher BMI and were less likely to be smokers than women with a spontaneous pregnancy. There was no significant difference in ethnicity or chronic disease frequency between pregnancies obtained with fertility treatment or spontaneously.

3.1. Fertility treatments vs. spontaneous conceptions and levels of placental biomarkers

The $\log_{10}$ PAPP-A MoM and $\log_{10}$ PlGF MoM were significantly lower in the fertility-treatment group compared to spontaneous pregnancies (difference = −0.011 [95%CI -0.019 to −0.003] and −0.018

Table 1
Characteristics of women with a spontaneous pregnancy or a pregnancy following fertility treatments.

Variable	Overall	Spontaneous pregnancies	Fertility treatment[b]	p-value[c]
	(n = 4815)	(n = 4388)	(n = 409)	
Maternal age, years[a]	28.9 ± 4.1	28.6 ± 4.0	31.4 ± 4.3	< 0.0001
BMI, kg/m^2[a]	25.0 ± 5.0	24.9 ± 4.9	25.9 ± 6.0	0.001
Smoking, n (%)	343 (7.1%)	330 (7.5%)	13 (3.2%)	0.0006
Ethnicity, n (%)				0.18
Caucasian	4621 (96.0%)	4206 (95.9%)	397 (97.1%)	
Afro-american	63 (1.3%)	61 (1.4%)	2 (0.5%)	
Asian	38 (0.8%)	35 (0.8%)	3 (0.7%)	
First Nations	8 (0.2%)	6 (0.1%)	2 (0.5%)	
Mixed	75 (1.6%)	71 (1.6%)	4 (1.0%)	
Chronic hypertension	23 (0.5%)	20 (0.5%)	3 (0.7%)	0.44
Pre-existing diabetes	8 (0.2%)	7 (0.2%)	1 (0.2%)	0.51

Legend: BMI = body mass index.
[a] Data are given as mean ± standard deviation.
[b] Ovulation agents, insemination or assisted reproductive technologies.
[c] Fisher exact tests or *t*-test.

Table 2
Mean and standard deviations of multiple of the medians of placental biomarkers according to subgroups of women with spontaneous pregnancy or pregnancy following fertility treatments (and their subtypes).

Biomarkers MoMs	Spontaneous pregnancies	Fertility treatment[a]	p[b]	Ovulation agents	Insemination	ART
	(n = 4388)	(n = 409)		(n = 233)	(n = 174)	(n = 85)
Log_{10} PAPP-A	1.00 ± 0.08	0.99 ± 0.07	0.004	0.99 ± 0.07	0.99 ± 0.08	0.98 ± 0.06*
Log_{10} PlGF	1.00 ± 0.12	0.98 ± 0.14	0.008	0.98 ± 0.14*	0.98 ± 0.14	0.96 ± 0.12*
Log_{10} sFlt-1	1.00 ± 0.06	1.00 ± 0.06	0.54	1.00 ± 0.06	1.00 ± 0.06	1.00 ± 0.06
Log_{10} AFP	1.00 ± 0.16	1.01 ± 0.16	0.42	1.01 ± 0.17	0.99 ± 0.15	1.04 ± 0.14
Log_{10} free β-hCG	1.00 ± 0.18	1.01 ± 0.19	0.51	0.99 ± 0.19	1.01 ± 0.17	1.05 ± 0.19*
Log_{10} UtA-PI	0.97 ± 0.63	1.05 ± 0.61	0.01	1.11 ± 0.56*	1.11 ± 0.60*	0.88 ± 0.72

*$p < 0.05$.
Legend: β-hCG = beta human chorionic gonadotropin, AFP = alpha-fetoprotein, ART = assisted reproductives technologies, MoM = multiples of the median, PAPP-A = plasma protein A, PlGF = placenta growth factor, sFlt-1 = solube fms-like tyrosine kinase-1, UtA-PI = uterine artery pulsatility index.
[a] Ovulation agents, insemination or assisted reproductive technologies.
[b] *t*-test.

[95%CI -0.032 to −0.005], respectively; Table 2; Fig. 1). After adjustment for covariates, PlGF levels remained significantly higher (−0.014 [95%CI -0.025 to −0.002]), but not PAPP-A levels (−0.006 [95%CI -0.013 to 0.002]) (Table 3). The log_{10} sFlt-1 MoM, log_{10} AFP MoM and log_{10} free β-hCG MoM were not significantly different between women who conceived spontaneously and those who used fertility treatments (Tables 2 and 3; Fig. 1).

The log_{10} UtA-PI MoM were higher in women with fertility treatments than those with spontaneous pregnancies (0.080 [95%CI 0.017 to 0.143]) (Table 2; Fig. 1) and remained significantly higher after adjustment (0.109 [95%CI 0.044 to 0.174]) (Table 3). Notching was present in 58.2% participants (n = 2553) with spontaneous pregnancies compared to 63.3% participants (n = 259) with fertility treatments (p = 0.046). Presence of notch remained significantly more frequent in women with fertility treatment in comparison with spontaneous pregnancies after adjustment (relative risk 1.16, 95%CI 1.08 to 1.26).

3.2. Types of fertility treatments and levels of placental biomarkers

The log_{10} PlGF MoM were significantly lower in women who received ovulation agents (Table 2), but this difference was not significant after adjustment for confounders (Table 3). No other maternal serum biomarkers were statistically associated with ovulation agents or insemination (Table 2; Table 3; Fig. 1). The log_{10} UtA-PI MoM were significantly higher in women who received ovulation agents or were inseminated compared to women with spontaneous pregnancies (Table 2; Fig. 1F), both in unadjusted and adjusted analyses (Table 3). Notching was more frequent in women who received ovulation agents (n = 162, 69.5%, p = 0.0006) or were inseminated (n = 117, 67.2%, p = 0.02) than women with spontaneous pregnancies. The relations remained significant after adjustment (relative risk of 1.24, 95%CI 1.14 to 1.35; and 1.27, 95%CI 1.15 to 1.42, respectively).

Women who used ART displayed significantly lower log_{10} PAPP-A MoM and log_{10} PlGF MoM and higher log_{10} free β-hCG MoM in comparison with spontaneous pregnancies (Table 2; Fig. 1) and the relation remained significant after adjustment for covariates (Table 3). The log10 UtA-PI MoM were not significantly different between women with ART or spontaneous pregnancies (Table 3), nor the notch presence (n = 41, 48.2%, p = 0.08; adjusted relative risk of 0.91, 95%CI 0.72 to 1.13).

3.3. Additional exploratory analyses

No markers were associated with sperm donation (Supplementary material Table e1). Metformin was reportedly used in 24 pregnancies (0.5%) and were not associated with any of the biomarkers (Supplementary material Table e1).

4. Discussion

We observed significant alterations in maternal serum biomarkers and doppler indices of placental function in the first trimester of pregnancy following fertility treatments in comparison to spontaneous pregnancies. Mean levels of PAPP-A and PlGF were significantly lower and levels of free β-hCG were significantly higher among ART pregnancies, but not in other subtypes of treatments. UtA-PI were higher and presence of notches was more frequent following both ovulation agents and insemination, but not ART.

Fertility treatments have been introduced in clinical practice with a limited knowledge of their potential impact on fetal and placental development. Association between abnormal angiogenic pattern and ART have been described previously [16,17], but the relation with other fertility treatments had not been thoroughly described.

Our results show that PlGF levels remained significantly lower during the first trimester in women who conceived through ART. This observation concurs with the results of a large study led by Pandya and colleagues [17] where similarly lower concentrations were observed among 312 IVF-pregnancies out of 11,414 singletons pregnancies. Considering the role PlGF plays in the angiogenesis, this difference could reflect an abnormal placentation caused by a restriction in the vessels' growth in pregnancies following assisted reproductive technologies [18]. Other authors have also previously observed lower levels of PAPP-A in ART pregnancies compared to spontaneous pregnancies [19,20]. Likewise, a recent systematic review observed lower PAPP-A levels in ART pregnancies compared to spontaneous pregnancies [9]. The levels of free β-hCG were not significantly different between ART and spontaneous pregnancies in this review, but ICSI pregnancies had higher levels than spontaneous pregnancies in subgroup analyses. Unfortunately, we did not distinguish between the different procedures encompassed within ART (such as conventional IVF and ICSI), precluding such subgroup analyses in our study. In a retrospective cohort analysis conducted in 2013, free β-hCG levels were similarly higher in both ICSI pregnancies and in cases of ART with donated oocyte than in spontaneous pregnancies [20]. Previous studies showed no difference between ART and spontaneous pregnancies for UtA-PI measured between 11 and 13^{+6} weeks of gestation [21,22], which concur with our observations. Hence, either procedures which are part of ART or the underlying cause(s) of infertility leading to ART have an impact on early placental development, without affecting vascular resistance and placental perfusion in the first-trimester of pregnancy.

In 2014, Mainigi and colleagues commented on the links between perturbations in maternal hormonal environment following ovarian stimulation and placental dysfunctions, especially the potential impact of gonadotropins on trophoblast differentiation and gene expression [6]. We observed a lower level of PlGF after ovulation stimulation or

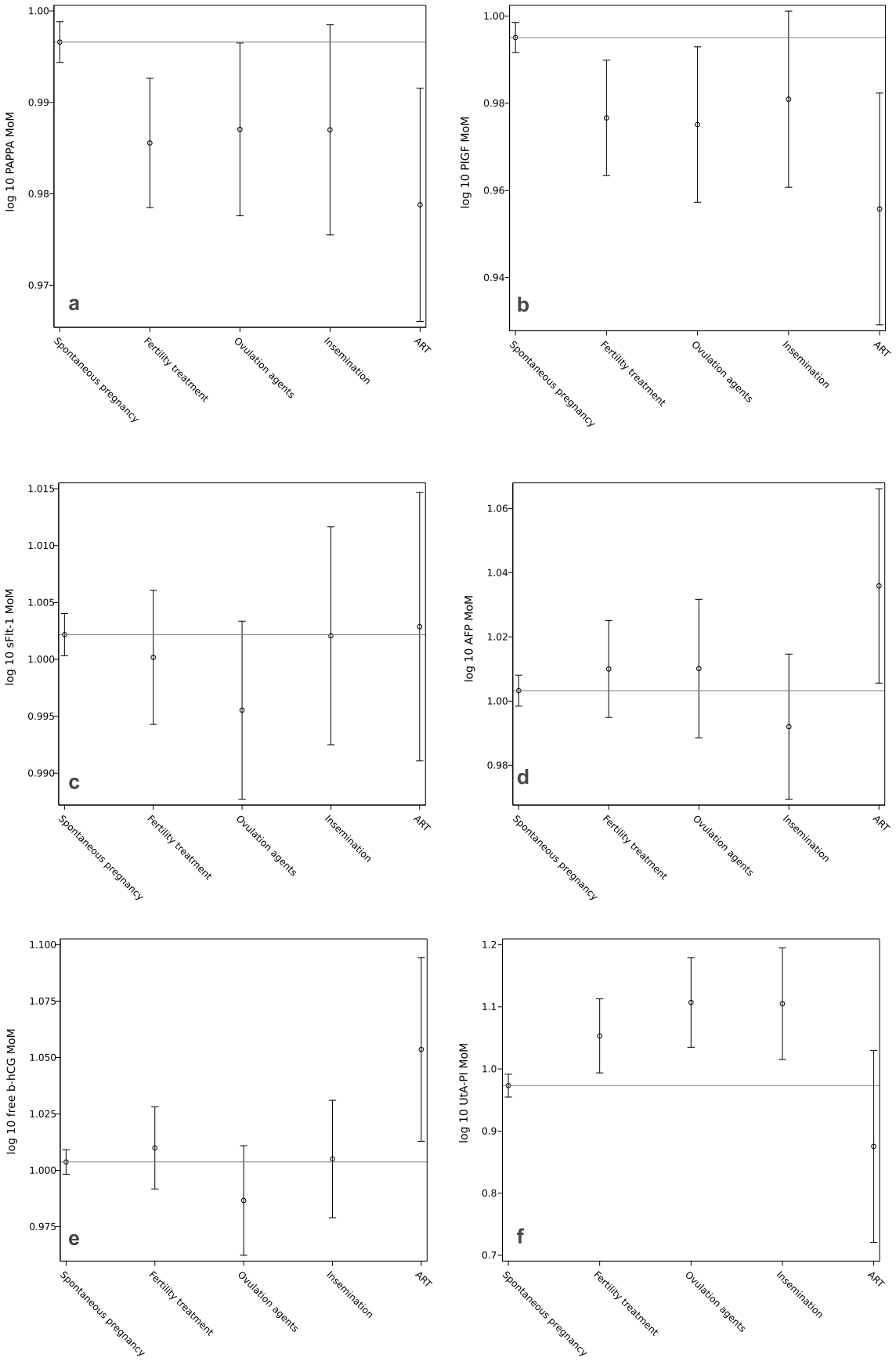

Fig. 1. Mean (and their 95% confidence intervals) of (A) $\log_{10}$ PAPP-A MoM, (B) $\log_{10}$ PlGF MoM, (C) $\log_{10}$ sFlt-1 MoM, (D) $\log_{10}$ AFP MoM, (E) $\log_{10}$ free β-hCG MoM or (F) $\log_{10}$ UtA-PI MoM for women who had spontaneous pregnancies, any fertility treatments, ovulation agents, insemination, ART, sperm donor or metformin use.

Table 3
Unadjusted and adjusted differences (and their 95% confidence intervals) in multiple of the medians between women with spontaneous pregnancy and women with pregnancy following fertility treatments (and their subtypes).

Biomarkers MoMs	Fertility treatment[a]		Ovulation agents	
	Unadjusted differences (95% CI)	Adjusted differences (95% CI)	Unadjusted differences (95% CI)	Adjusted differences (95% CI)
Log_{10} PAPP-A	−0.011 (−0.019, −0.003)	−0.006 (−0.013, 0.002)	−0.010 (−0.020, 0.0004)	−0.002 (−0.011, 0.007)
Log_{10} PlGF	−0.018 (−0.032, −0.005)	−0.014 (−0.025, −0.002)[b]	−0.020 (−0.038, −0.002)	−0.011 (−0.026, 0.004)
Log_{10} sFlt-1	−0.002 (−0.008, 0.004)	0.001 (−0.006, 0.007)	−0.007 (−0.015, 0.002)	−0.003 (−0.011, 0.005)
Log_{10} AFP	0.007 (−0.010, 0.023)	0.012 (−0.004, 0.029)	0.007 (−0.015, 0.028)	0.016 (−0.006, 0.037)
Log_{10} free β-hCG	0.006 (−0.013, 0.025)	0.015 (−0.003, 0.034)	−0.017 (−0.041, 0.007)	−0.005 (−0.029, 0.019)
Log_{10} UtA-PI	0.080 (0.017, 0.143)	0.109 (0.044, 0.174)[b]	0.134 (0.059, 0.208)	0.162 (0.079, 0.244)[b]

Biomarkers MoMs	Insemination		ART	
	Unadjusted differences (95% CI)	Adjusted differences (95% CI)	Unadjusted differences (95% CI)	Adjusted differences (95% CI)
Log_{10} PAPP-A	−0.010 (−0.021, 0.002)	0.002 (−0.009, 0.012)	−0.018 (−0.031, −0.005)	−0.024 (−0.039, −0.009)[b]
Log_{10} PlGF	−0.014 (−0.035, 0.006)	−0.011 (−0.028, 0.007)	−0.040 (−0.064, −0.014)	−0.038 (−0.062, −0.013)[b]
Log_{10} sFlt-1	0.000 (−0.010, 0.009)	0.006 (−0.003, 0.015)	−0.001 (−0.013, 0.014)	−0.003 (−0.016, 0.011)
Log_{10} AFP	−0.011 (−0.036, 0.013)	−0.003 (−0.028, 0.022)	0.033 (−0.002, 0.068)	0.029 (−0.006, 0.065)
Log_{10} free β-hCG	0.001 (−0.027, 0.029)	0.018 (−0.010, 0.046)	0.050 (0.011, 0.089)	0.048 (0.009, 0.088)[b]
Log_{10} UtA-PI	0.132 (0.037, 0.227)	0.169 (0.073, 0.266)[b]	−0.098 (−0.236, 0.037)	−0.082 (−0.219, 0.055)

Adjusted for maternal age, body mass index, smoking, ethnicity, pre-existing hypertension and diabetes.
Legend: β-hCG = beta human chorionic gonadotropin, AFP = alpha-fetoprotein, ART = assisted reproductives technologies, MoM = multiples of the median, PAPP-A = plasma protein A, PlGF = placenta growth factor, sFlt-1 = solube fms-like tyrosine kinase-1, UtA-PI = uterine artery pulsatility index.
[a] Ovulation agents, insemination or assisted reproductive technologies.
[b] Remained statistically significant after using spline to modelize maternal age and BMI.

induction, but that relation did not remain significant after adjustment for maternal age, body mass index, smoking, ethnicity, and pre-existing hypertension and diabetes. We did not identify significant differences in the levels of other placental biomarkers in women who used non-ART fertility therapies in comparison to women with spontaneous pregnancies, except higher vascular resistance in uterine arteries. Women who require ovulation induction are mostly suffering polycystic ovarian syndrome, which has been associated with higher uterine vascular resistance both prior to and during pregnancy [23–26]. Hence, the pathophysiology leading to the use of ovulation agents might explain the relationship observed in our study.

4.1. Strengths and limitations

A strength of our study comes from gathering data from a very large cohort of nulliparous women and study of both ART and non-ART fertility therapies. We also took in consideration the variations in PAPP-A, PlGF, sFlt-1, AFP and free β-hCG concentrations, as well as UtA-PI measurements and notches with gestational age, and conducted adjusted analyses to control for potential confounders such as maternal age, BMI, smoking, ethnicity, pre-existing hypertension and diabetes.

Our study is a secondary analysis of a cohort in which data on medical and obstetrical history were collected from a questionnaire, being therefore subject to information bias. Fertility treatments were self-reported and treatment options other than ART, ovulation agents and insemination were not systematically questioned, hence possibly underreported. Non-diagnosed preclinical hypertension or diabetes mellitus might have led to an underestimation of the frequency of such diseases and incomplete control for confounding. Considering serum biomarkers and doppler measurements were conducted by trained research personnel unaware of the participants use of fertility treatments and the validity of the biomarker measurements, the risk of measurement error was considered low. If misclassification occurred, it would be nondifferential. Moreover, although we considered maternal age, BMI, ethnicity, smoking habit and chronic diseases such as hypertension and diabetes as cofactors for adjustment, residual confounding due to other variables related to both fertility treatments and biomarkers is possible.

Furthermore, we did not have information on the causes and the duration of infertility, the number of cycles of treatment nor the treatment regimen. Hence, we could not explore how such factors might have influenced the entry into the study or impacted on our results. We chose to group all treatment options and to compare any treatment to spontaneous pregnancies although the underlying pathologies and the association of each type of treatment with hormonal profiles and immunologic responses might differ. Also, only few participants reported having resorted to options other than ovulation stimulation/induction, insemination and/or ART, and no additional details were collected on fertility treatments, precluding exploration of the effects of specific procedures. Additional information such as oocyte donation, ICSI, intracervical or intrauterine insemination, ovulation stimulation vs. Induction, use of GnRH agonist or hCG for triggering ovulation, etc. could have allowed for a more precise study of the relations between different treatment options and placental function. Few women reported using metformin as fertility treatment, thus the low power of our exploratory analyses might have resulted in a type II error.

Although we observed statistically significant differences, some were clinically minimal (e.g., adjusted reduction of PlGF by 0.01 MoM in women who underwent fertility treatment). However, our findings support the hypothesis of a correlation between fertility treatments and alterations of the placental function. The magnitude of the alterations varied at the individual level, yet the findings are consistent with the reported increased risk of placenta-mediated complications in women who underwent fertility treatments [27–31]. Our results also inform on differences in the pattern of placental function alterations according to the types of fertility treatments.

Finally, our study does not allow to establish causality and the association observed between fertility treatments and markers of

placental function could be a result of the impact of treatments on the placental development or a common cause of infertility and placental dysfunctions.

5. Conclusions

In conclusion, our results suggest that fertility treatments are correlated with alterations of placental development in early pregnancy. Further examination of the relation between fertility treatments and placentation and exploration of potential common pathophysiological mechanisms between infertility and placental dysfunction are needed. Exploration of the association between different procedures and placental biomarkers could also shed light on the relationships observed in our cohort. A better understanding of the relation between the mode of conception and placentation might improve the identification of pregnancies at high risk of complications and lead to better care for pregnant women and their fetuses.

Roles of authors

AB and EB contributed to the conception and design of the study. AC, AB, CG and EB contributed to the acquisition of the data. AC and AB analysed the data. All authors participated in the interpretation of the results. AC and AB drafted the article. All authors critically revised the manuscript for important intellectual content and approved the final version.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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