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Uterine artery Doppler pulsatility index at 11–38 weeks in ICSI pregnancies with egg donation

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Abstract

Background: Uterine artery Doppler pulsatility index (UtA-PI) may be different in pregnancies with egg donation (ICSI-ED) as compared to conceptions with autologous intra-cytoplasmatic sperm injection (autologous ICSI) and to spontaneous conceptions (SC).
Methods: One hundred and ninety-four pregnant women with different modes of conception (MC) were prospectively evaluated: 53 ICSI-ED, 36 autologous ICSI and 105 SC. To evaluate the effects of different MC on PI, multivariable linear regression (MLR) models predicting UtA-PI were fitted after adjustment for maternal age, body mass index, race, parity, smoking status and gestational age.
Results: In the first trimester, at MLR, autologous ICSI was not associated with a significantly different UtA-PI [estimate (EST) 0.01; 95% confidence interval (CI) −0.19, 0.2; P=0.9] when compared to SC. Conversely, MC by ICSI-ED was associated with lower first trimester UtA-PI (EST −0.32; CI −0.55, −0.08; P=0.01) when compared to SC. At MLR, MC by autologous ICSI and by ICSI-ED were not associated with significant differences in the second and third trimester UtA-PI when compared to SC.
Conclusion: ICSI-ED conception presented lower UtA-PI when compared to SC at 11^{+0}–13^{+6} weeks but not at later assessments. Correction of UtA-PI measurement specifying the origin of oocyte may be useful in first trimester screening.

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Keywords: Egg donation (ED); intra-cytoplasmatic sperm injection (ICSI); *in vitro* fertilization (IVF); pulsatility index; uterine artery Doppler.

Introduction

Pre-eclampsia (PE) is associated with impaired invasion of the trophoblast through the spiral arteries, which is manifested as increased impedance to flow in the uterine arteries (UtA) [1]. PE is one of the major causes of maternal mortality and fetal morbidity [2]. The incidence of PE is increased in *in vitro* fertilized (IVF) pregnancies [3] and it is particularly high in heterologous IVF pregnancies by egg donation (ED) compared to spontaneous conceptions [4]. A combination of maternal demographic characteristics, uterine artery pulsatility index (PI), mean arterial pressure (MAP), maternal serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11^{+0}–13^{+6} weeks' gestation can identify a high proportion of pregnancies at high-risk for preterm PE [5, 6]. Two recent meta-analysis of randomized studies reported that low-dose aspirin started at or before 16 weeks was associated with a 50% reduction in the overall risk for PE and an 80% reduction in preterm PE [7, 8]. However, these data are not providing definitive conclusions to be drawn and these results are being tested in a prospective major randomized trial (ASPRE: Combined Multi-Marker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention [9]).

Previous studies did not find any differences in UtA pulsatility index (UtA-PI) of assisted reproductive technologies (ART) pregnancies when compared to spontaneous pregnancies [10, 11], however no distinction was made between autologous IVF and donor oocytes IVF in which the risk of PE is also higher [4].

Tayyar et al. [12] elaborated a model to express UtA-PI multiples of the median (MoMs) in which significant independent contributions to PI were provided by gestational age, maternal age and weight, racial origin, history of PE and birth weight in the last pregnancy. In this study method of conception was assessed as spontaneous, ovulation induction or IVF, without distinguishing the origin of oocyte (autologous ICSI vs. ICSI-ED) and the results show that method of conception did not affect UtA-PI.

The hypothesis of this study is that uterine perfusion in ICSI-ED pregnancies is different from that in autologous ICSI and spontaneous pregnancies. We tested this hypothesis comparing UtA-PI of spontaneous, autologous ICSI and ICSI-ED pregnancies in the first, second and third trimester.

Materials and methods

Study population

The current study relied on a prospectively collected database of 194 consecutive pregnant women enrolled between 2010 and 2015 at two tertiary care centres, with different modes of conception defined as spontaneous conception, autologous ICSI from fresh transfer and heterologous by ICSI-ED. Exclusion criteria consisted of non-singleton pregnancy, aneuploidies, history of pre-eclampsia, history of hypertension or diabetes and auto-immune disease. Due to the fact that egg donations are obtained by ICSI, we included only ICSI procedures. All women undergoing first trimester screening routinely provided informed consent for their clinical data and anonymized records to be used for research purposes in general. Local Institutional Review Board approvals for the use of clinical data for research studies were obtained.

Outcome

The outcome of the study was UtA-PI, defined as (peak systolic velocity – end diastolic velocity) / time averaged velocity.

UtA-PI was assessed in the first trimester at 11^{+0}–13^{+6} weeks' gestation, in the second trimester at 14^{+0}–23^{+6} weeks' gestation and in the third trimester at 24^{+0}–37^{+6} weeks' gestation. First, second and third-trimester Doppler studies were conducted trans-abdominally. In the first trimester, a sagittal section of the uterus was obtained and the cervical canal and internal cervical os were identified. The transducer was tilted gently from side to side and color-flow mapping was used to identify each UtA along the side of the cervix and the uterus, at the level of the internal os [13–15].

In the second and third trimesters the UtAs were identified using color Doppler, at the apparent crossover with the external iliac arteries.

After identification of each UtA, pulsed-wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel. Care was taken to ensure that the angle of insonation was less than 20° and the peak systolic velocity was greater than 60 cm/s to ensure that the UtA, rather than the arcuate artery, was being examined. When three similar waveforms had been obtained consecutively, the PI was measured tracing manually the contour of three similar waves and the mean PI of the left and right arteries was calculated. All Doppler studies were carried out by sonographers with extensive experience in obstetrics ultrasound and a Certificate of Competence in Doppler studies by the Fetal Medicine Foundation (FMF).

Covariates

Covariates consisted of maternal age at conception, body mass index (BMI), race (classified as Caucasian vs. others), parity (classified as nulliparity vs. multiparity), smoking status (classified as no vs. yes) and gestational age at UtA-PI assessment.

Statistical analyses

Statistical analyses, reporting and interpretation of the results were conducted in three steps. First, medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann-Whitney and Fisher's Exact test were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively. Box and whisker plot was used to depict the first trimester UtA-PI according to mode of conception.

Second, multivariable linear regression analysis was used to assess the impact of mode of conception on first, second and third trimester UtA-PI after adjustment for all the available covariates, namely maternal age, BMI, race, parity, smoking status and gestational age.

Third, given the longitudinal nature of our study, cubic smoothing spline method was used to graphically explore UtA-PI changes according to gestational age in the overall population as well as according to mode of conception.

Furthermore, in order to control for the potential effect of gestational age according to previously published normative data on uterine artery pulsatility index values, the linear regression analysis was repeated after conversion of the Uta-PI to z-scores [16].

All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0 [17] with the packages *Hmisc*, *stats*, *rms*, and *graphics*. All tests were two-sided with a significance level set at $P < 0.05$.

Results

Patient characteristics

Overall, 194 patients were included in the study (Table 1). Mode of conception was spontaneous in 105 patients (54%), by autologous ICSI in 36 (19%) and by ICSI-ED in 53 (27%). Compared to patients who conceived spontaneously, patients who conceived by autologous ICSI and by ICSI-ED were significantly older (all $P < 0.001$).

Only two patients (1%) developed PE and they were both in the ICSI-ED group. One of them developed a liver rupture due to haematoma at 35 weeks of gestational age.

Table 1: Descriptive characteristics of 194 patients investigated with uterine artery Doppler mean pulsatility index stratified according to mode of conception (spontaneous, autologous intra-cytoplasmatic sperm injection or egg donation).

Variable	Overall (n = 194)	Spontaneous conception (n = 105)	ICSI conception (n = 36)	P-value	Spontaneous conception (n = 105)	Egg donation conception (n = 53)	P-value
Maternal age							
Median	36	33	38	< 0.001	33	44	< 0.001
IQR	31–41	29–35	34–40		29–35	40–46	
BMI[a]							
Median	21.7	21.5	22.2	0.4	21.5	22.4	0.3
IQR	19.9–23.7	19.8–23.4	20–23.9		19.8–23.4	20.2–24.6	
Race							
Caucasian	182 (94)	96 (91)	34 (94)	0.2	96 (91)	52 (98)	0.7
Parity							
Nulliparous	170 (88)	87 (83)	33 (92)	0.3	87 (83)	50 (94)	0.049
Smoking							
No	179 (93)	93 (89)	34 (95)	0.5	93 (89)	52 (98)	0.06

Data presented as frequencies and percentages unless otherwise specified.
[a]Missing for seven cases.
PI = Uterine artery Doppler mean pulsatility index defined as (peak systolic velocity – end diastolic velocity)/time averaged velocity; ICSI = autologous intra-cytoplasmatic sperm injection; IQR = interquartile range.

Furthermore, the proportions of pathological UtA-Pi (above the 95th centile for gestational age) in all three trimesters were 3.8% in the spontaneous group, 3.7% in the autologous ICSI group and 3.7% in the ICSI-ED group. in particular, those patients who showed a pathological UtA-PI in the first trimester, maintained this pattern also in the second and third trimesters.

First trimester uterine artery pulsatility index

The first trimester median UtA-PI was 1.65 [inter-quartile range (IQR) 1.33–2.05] in patients who conceived spontaneously, 1.64 (IQR 1.27–2.06) in patients who conceived by autologous ICSI and 1.28 (IQR 1.03–1.78) in patients who conceived by ICSI-ED (Figure 1).

At multivariable linear regression analysis adjusted for all the available covariates (Table 2), mode of conception by autologous ICSI was not associated with first trimester UtA-PI [estimate (EST) 0.01; 95% confidence interval (CI) – 0.19, 0.2; P = 0.9] when compared to spontaneous conception. Conversely, mode of conception by ICSI-ED was associated with lower first trimester UtA-PI (EST – 0.32; CI – 0.55, – 0.08; P = 0.01) when compared to spontaneous conception. Of note, multiparity was associated with higher first trimester UtA-PI (EST 0.23; CI 0.02, 0.44; P = 0.03) when compared to nulliparity. Similar results were observed after conversion of all UtA-PI values to z-scores (Table 3).

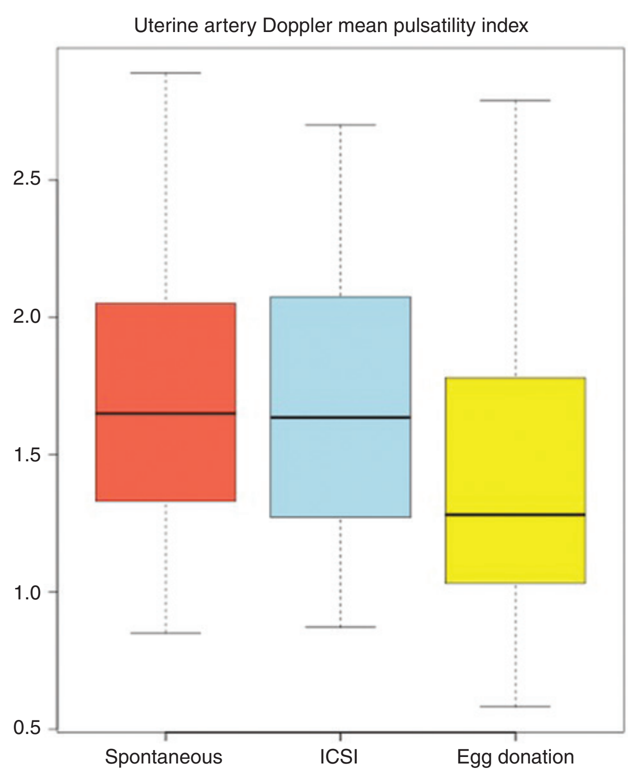

Figure 1: Box and Whisker plot depicting uterine artery Doppler mean pulsatility index in the first trimester stratified according to the mode of conception in 194 patients investigated with uterine artery Doppler, 2010–2015. Uterine artery Doppler mean pulsatility index defined as (peak systolic velocity – end diastolic velocity)/ time averaged velocity. ICSI = autologous intra-cytoplasmatic sperm injection.

Table 2: Linear regression analysis predicting uterine artery Doppler mean pulsatility index according to mode of conception in 194 patients investigated with uterine artery Doppler in the first trimester, 2010–2015.

Predictors	Multivariable linear regression predicting uterine artery Doppler mean pulsatility index	
	Estimate (95% CI)	P-value
Mode of conception		
Spontaneous	Ref	–
Autologous ICSI	0.01 (– 0.19; 0.20)	0.9
Egg donation	– 0.32 (– 0.55; – 0.08)	0.01
Maternal age (years)	0.004 (– 0.01; 0.02)	0.6
Body mass index (kg/m^2)	– 0.01 (– 0.03; 0.01)	0.1
Race		
Caucasian	Ref	–
Others	0.07 (– 0.21; 0.36)	0.6
Parity		
Nulliparity	Ref	–
Multiparity	0.23 (0.02; 0.44)	0.03
Smoking status		
No	Ref	–
Yes	– 0.2 (– 0.45; 0.06)	0.1
Gestational age (days)	– 0.01 (– 0.03; 0.01)	0.2

Uterine artery Doppler mean pulsatility index defined as (peak systolic velocity – end diastolic velocity)/time averaged velocity.
Estimate: modification in uterine artery Doppler mean pulsatility index units.
CI = Confidence intervals; ICSI = autologous intra-cytoplasmatic sperm injection.

Table 3: Linear regression analysis predicting uterine artery Doppler mean pulsatility index expressed as z-score according to mode of conception in 194 patients investigated with uterine artery Doppler in the first trimester, 2010–2015.

Predictors	Multivariable linear regression analysis predicting uterine artery Doppler mean pulsatility index expressed as z-score	
	Estimate (95% CI)	P-value
Mode of conception		
Spontaneous	Ref	–
Autologous ICSI	0.004 (– 0.19; 0.20)	1
Egg donation	– 0.31 (– 0.54; – 0.08)	0.01
Maternal age (years)	0.004 (– 0.01; 0.02)	0.6
Body mass index (kg/m^2)	– 0.02 (– 0.03; 0.01)	0.1
Race		
Caucasian	Ref	–
Others	0.07 (– 0.22; 0.36)	0.6
Parity		
Nulliparity	Ref	–
Multiparity	0.23 (0.02; 0.44)	0.03
Smoking status		
No	Ref	–
Yes	– 0.2 (– 0.45; 0.06)	0.1

Estimate: modification in uterine artery Doppler mean pulsatility index units.
CI = Confidence intervals; ICSI = autologous intra-cytoplasmatic sperm injection.

Second and third trimester uterine artery pulsatility index

Overall (Figure 2), the second trimester median UtA-PI resulted 0.87 (IQR 0.68–1.15) and the third trimester median UtA-PI resulted 0.69 (IQR 0.57–0.82).

When stratified according to mode of conception, the second trimester UtA-PI was 0.91 (IQR 0.72–1.15) in patients who conceived spontaneously, 1.02 (IQR 0.83–1.49) in patients who conceived by autologous ICSI and 0.76 (IQR 0.61–0.96) in patients who conceived by ICSI-ED (Figure 3). At multivariable linear regression analysis adjusted for all the available covariates, mode of conception by autologous ICSI (EST 0.16; CI – 0.04, 0.4; P = 0.1) and by ICSI-ED (EST – 0.19; CI – 0.4, 0.03; P = 0.08) were not associated with second trimester UtA-PI when compared to spontaneous conception.

The third trimester median UtA-PI was 0.76 (IQR 0.63–0.90) in patients who conceived spontaneously, 0.72 (IQR 0.61–0.82) in patients who conceived by autologous ICSI and 0.58 (IQR 0.52–0.70) in patients who conceived by ICSI-ED (Figure 3). At multivariable linear regression

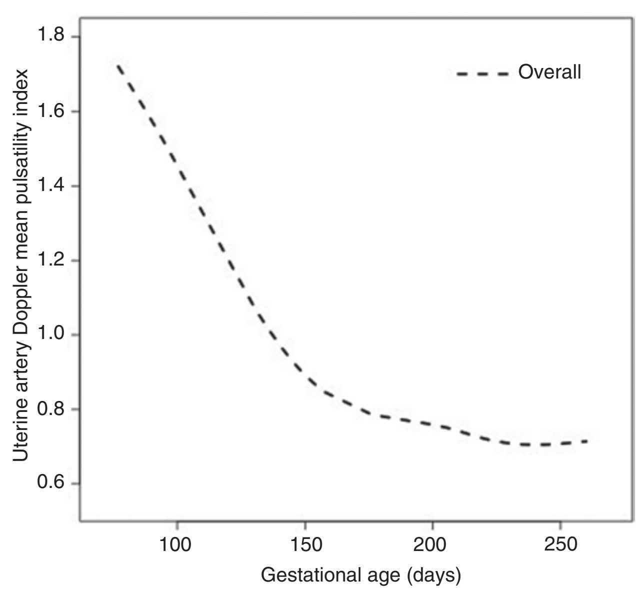

Figure 2: Uterine artery Doppler mean pulsatility index change plotted against gestational age in the overall population of 194 patients investigated with uterine artery Doppler, 2010–2015. Uterine artery Doppler mean pulsatility index defined as (peak systolic velocity – end diastolic velocity)/time averaged velocity.

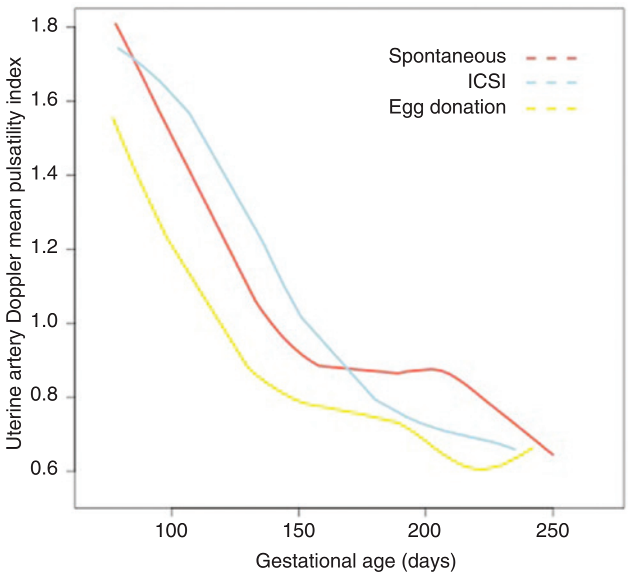

Figure 3: Uterine artery Doppler mean pulsatility index change plotted against gestational age stratified according to mode of conception in 194 patients investigated with uterine artery Doppler, 2010–2015. Uterine artery Doppler mean pulsatility index defined as (peak systolic velocity – end diastolic velocity)/time averaged velocity. ICSI = autogous ICSI.

analysis adjusted for all the available covariates, mode of conception by autologous ICSI (EST −0.07; CI −0.23, 0.09; P = 0.4) and by ICSI-ED (EST −0.16; CI −0.34, 0.02; P = 0.08) was not associated with third trimester UtA-PI when compared to spontaneous conception.

Discussion

The results of this study confirmed the hypothesis showing that uterine perfusion examined by uterine Doppler studies and measured by PI is different in pregnancy with ICSI-ED as compared to autologous ICSI and spontaneous conceptions. ED conception was associated with a lower UtA-PI at 11–14 weeks, after adjustment for all covariates. A similar but non-significant trend was also noted in the second and in the third trimester.

As previously stated, these findings are not negligible with respect to clinical significance. Effective use of UtA-PI necessitates correction for maternal characteristics and medical history, which are affecting the measurement. From our results, mode of conception appears as a further variable to consider when calculating MoMs for egg donations.

The current study found different results if compared with the first studies by Prefumo et al. [10] and Carbone et al. [11], since they did not find any differences in UtA pulsatility index (UtA-PI) when comparing IVF pregnancies to spontaneous pregnancies. However, the mentioned studies had different designs, and did not distinguish between autologous ICSI and ICSI-ED, classifying these two categories in the same group named "IVF".

A recent study [18] compared UtA-PI MoMs adjusted for gestational age, body mass index and maternal ethnicity only in the first trimester differentiating between these three groups: ED, ICSI and spontaneous conceptions. This study did not find any difference in UtA-PI between the groups. However, the authors did not calculate UtA-PI MoMs of their study groups from their reference population but from an algorithm derived from a previously published study population, after adjusting for few of the major confounders [12]. The model by Tayyar et al. expressed UtA-PI as MoMs, in which significant independent contributions to PI were provided by maternal age, gestational age, weight, racial origin, a history of PE in the previous pregnancy and birth weight in the last pregnancy. In this study method of conception was assessed as spontaneous, ovulation induced or IVF, without distinguishing in this last group the origin of oocyte (autologous vs. heterologous); in this way method of conception seemed not to affect UtA-PI levels.

The results of our study differentiate with a rigorous statistical methodology UtA-PI of egg donation as compared to spontaneous and autologous ICSI. In fact, MoMs of our study groups were defined using our reference population of normal pregnancies with spontaneous conception and correcting for most of the confounders defined by Tayyar et al. [12].

One of the different hypothesis suggested to explain the increased incidence of PE in egg donation pregnancies involves a peculiar response of the recipient to trophoblast antigens of the egg donor or vice versa [19]. This abnormal cross talk and immune response may be either secondary to the different maternal endocrine characteristics of women undergoing IVF or to the presence of foreign antigens as it is the case with donor oocytes. Our results indicate that uterine perfusion is apparently higher in these women in the first trimester. Explanations of this finding may be related to the high estrogens provided to these women and the consequent disregulation in extravillous trophoblast migration and remodelling of the uterine spiral arteries [20]. Furthermore, as stated by Thilaganathan in 2016 [21], PE might be the consequence of the inability of the maternal cardiovascular system to cope with the significant volume load of pregnancy. Thus, considering the subgroup of egg-donated women, PE may present a different pathogenesis: an impaired maternal cardiovascular function might be the origin of PE rather than an impaired placentation (detected by UtA-PI).

During longitudinal evaluation, this difference disappeared in the second and third trimester, in which UtA-PI levels of egg donation conceptions remained lower than spontaneous and ICSI conception, although not reaching statistically significant differences. As expected, maternal age was significantly higher in our ED group than in the other groups. Uterine perfusion has been shown to be affected by maternal age [6]. It is reasonable to believe that aging of the mother will affect this and many other physiological variables, such as arterial blood pressure or hepatic and renal metabolism of some hormones. However, the impact of maternal age in our study was not statistically significant in the regression model, probably due to the effect of small sample size. Significance of differences of UtA-PI in our study groups was maintained even after correcting for maternal age.

The current study is not devoid of limitations. First and foremost, a significant limitation is related to the low number of cases. Further prospective studies including the mode of conception into a predictive model are needed in order to investigate deeply the trend of the uterine flows, in particular of those patients who will show abnormal UtA-PI without a clinical impact and vice versa. Nonetheless, despite this limitation, the findings of the current study require special consideration since, for the first time, the impact of the mode of conception on the UtA-PI in the three trimesters was evaluated distinguishing the origin of the oocyte. ART pregnancy represents a very heterogeneous group of pregnancies including ovulation induction, *in vitro* fertilization, *in vitro* fertilization with ICSI; moreover, each procedure may be performed with the use of cleavage stage embryos or blastocyst, with or without the use of cryopreservation techniques. Our group has previously shown the impact of cryopreservation of blastocyst on the measurement of the nuchal translucency, which appears significantly increased in this subgroup [22]. Moreover, we have recently reported altered first trimester maternal serum placenta marker levels in ED as well as in autologous IVF/ICSI pregnancies [23].

In conclusion, pregnancies conceived with egg donation presented lower UtA-PI at 11^{+0}–13^{+6} weeks' when compared to spontaneous conception, after adjustment for maternal age, BMI, race, parity, smoking status and gestational age.

Our study suggests that ART pregnancies are a heterogeneous group of pregnancies, which deserve further classification and study. Correction of UtA-PI MoMs specifying the origin of oocyte (autologous ICSI or egg donation) may be useful in risk assessment and screening algorithms.

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Author's statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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