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# Correlation between first trimester placental growth factor levels and skin microvascular reactivity assessed by laser speckle contrast imaging - a cross-sectional study

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ABSTRACT

*Objectives:* To investigate the association between first-trimester placental growth factor (PlGF) levels and maternal skin microvascular reactivity, as assessed by laser speckle contrast imaging (LSCI) combined with post-occlusive reactive hyperemia. Additionally, to explore the correlations between maternal microvascular function and other first-trimester serum biochemical and biophysical markers.

*Methods:* Fifty-three patients carrying a singleton gestation were enrolled during their routine first trimester scan. Skin blood flux at the dorsal hand was recorded using LSCI before, during, and after a 3-min arterial occlusion. Microvascular reactivity parameters were calculated and compared with maternal serum biochemical markers (PlGF, pregnancy-associated plasma protein A [PAPP-A], and free beta-human chorionic gonadotropin [free β-hCG]), expressed as multiples of the median, and with maternal biophysical markers.

*Results:* PlGF levels showed a moderate positive correlation with base-to-peak flux (r = 0.51, 95 % confidence interval, CI, 0.27–0.69) and a weak but statistically significant positive correlation with peak flux (r = 0.31, 95 % CI 0.04–0.59).

PAPP-A levels above the median were associated with higher base-to peak flux compared to PAPP-A below the median (253.41 % versus 215.08 %, p = 0.02). A moderate positive correlation was also found between free β-hCG and peak flux (r = 0.4, 95 % CI 0.15–0.60). No correlations were found between the parameters of hyperemic response and maternal biophysical markers.

*Conclusions:* Maternal first-trimester skin microvascular reactivity indices correlate positively with serum placental biomarker levels, particularly PlGF. This suggests that maternal peripheral microvascular function, assessed by LSCI, may reflect placental microcirculation. Further studies are warranted to determine whether this tool could serve as an early marker of placental function.

## 1. Introduction

Early successful placentation is characterized by a rapid sequence of angiogenesis phenomena under the local control of growth factors [1,2]. This process necessitates a tight balance between proangiogenic and antiangiogenic factors [3]. Multiple studies have reported that there is an angiogenic imbalance in pregnancies complicated by preeclampsia and fetal growth restriction (FGR) [4–7]. In such pregnancies, the concentrations of proangiogenic factors are decreased in the maternal circulation, whereas antiangiogenic factors are increased [6,7].

Placental growth factor (PlGF) is an increasingly important molecule in the prediction, diagnosis and treatment of preeclampsia and FGR [5,8,9]. The PlGF has a marked proangiogenic activity that impacts the feto-placental circulation, promotes the development and maturation of the placental vascular system, increases the proliferation and reduces the apoptosis of trophoblast cells [8].

Low circulating PlGF levels precede the clinical manifestation of preeclampsia and FGR [2,4,7,8]. Reduced PlGF levels are probably both

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a consequence of abnormal early placentation and a contributing factor to continued abnormal growth during the latter half of pregnancy [8]. Since placental dysfunction appears to originate in the first trimester, this represents an appropriate time window for research on the early mechanisms that influence placental development [2,10,11].

Laser speckle contrast imaging (LSCI) is a novel, non-invasive tool for assessing skin microvascular perfusion in real-time [12,13]. Previous studies have established that skin microcirculation and its alterations are correlated with changes in other microvascular beds, such as the renal and the retinal beds, and are associated with cardiovascular diseases [14–16]. However, knowledge is lacking with respect to whether this also applies to the placenta [17].

The main purpose of this cross-sectional study was to assess the correlation between maternal skin microvascular reactivity, using LSCI combined with post-occlusive reactive hyperemia, and first trimester PlGF levels. Additionally, the correlations between the maternal microvascular function and other first trimester serum biochemical and biophysical markers of placental function were investigated.

## 2. Materials and methods

### 2.1. Population

This cross-sectional study was conducted at the Department of Obstetrics and Gynecology of Careggi University Hospital in Florence Italy, between November 2022 and March 2024. This investigation was part of a prospective observational study on microvascular function in physiologic and pathologic pregnancies.

This study was performed according to the principles of the Declaration of Helsinki and was approved by the ethics committee of Careggi University Hospital on 04/10/2022 (reference number 22853_oss). Written informed consent was obtained from all the participants.

The study population included patients carrying a singleton pregnancy undergoing routine first-trimester combined screening for aneuploidies and preeclampsia screening, using the Fetal Medicine Foundation algorithm [18].

Exclusion criteria were pre-existing hypertension, cardiovascular or renal disease, type I or II diabetes mellitus, current smoking habit, a body mass index >35 kg/m$^2$, and maternal age over 45 years.

### 2.2. Serum biochemical and biophysical markers assessment

Gestational age was confirmed by crown–rump length measurement between 11 + 0 and 13 + 6 weeks of gestation. Maternal serum biomarkers were measured between 11 and 13 + 6 weeks. PlGF, Pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (free β-hCG) levels were assessed. For all biomarkers, the multiples of the median (MoM) were calculated as a measure of the deviation of individual results from the median according to gestational age, as serum biochemical markers concentrations are highly related to gestational age [19]. To explore the significance of serum biomarkers, MoM levels were further categorized as low (below the median) or high (above the median).

Ultrasound examinations were performed with a Voluson E10 ultrasound machine (GE Medical Systems, Kretz Ultrasound, Zipf, Austria) with a 3.5–5.0 MHz abdominal probe. The uterine arteries were examined at their apparent crossing with the external iliac artery. The pulsatility index (PI) and PI percentile were calculated.

Mean arterial pressure (MAP) was measured by taking the average of two measurements in both arms [20].

### 2.3. Skin microvascular function assessment

Microvascular skin blood flow was assessed using LSCI (PeriCam PSI system, Perimed, Järfälla, Sweden). This method involves scanning the skin's surface with an invisible near infra-red laser (785 nm). A diffuser spreads the laser beam across the measurement area, creating a speckle pattern. The blood perfusion was calculated by analysing temporal and spatial variations in this speckle pattern. The median laser flux was calculated for each image using a dedicated image-processing software (PeriSoft, Perimed, Järfälla, Sweden) and was expressed in arbitrary Prefusion Units (PU).

In each patient the LSCI study was performed on the same day of the first trimester ultrasound in a temperature-controlled environment (24 °C). Caffeine-containing drinks were not allowed for 2 h before the test, as caffeine acutely improves endothelium-dependent microvascular responses [21].

The microvascular skin blood flow at the dorsal face of the hand was recorded (Fig. 1A), while the participant rested in a semi-recumbent position with the arm supported by a pillow. After measuring the woman's blood pressure, a postocclusive reactive hyperemia (PORH) protocol was performed with a pneumatic cuff attached to the bicep. Following a 2-min baseline measurement, the pneumatic cuff was inflated to a pressure of at least 40 mmHg above the systolic blood pressure. The occlusion time was set at 3 min. This duration was chosen since it produces a greater postocclusive reactive hyperemia compared to shorter duration [22]. Following immediate cuff release, the changes in microcirculation flux (the hyperemic response) were recorded for 4 min. Fig. 1B illustrates an example of the recording.

The peak flux was calculated using the image-processing software. This parameter represents the highest flux value at the post-occlusive period (expressed in arbitrary PU). The base-to-peak flux is the percentage increase of flux from baseline to the maximal post-occlusive response [(peak - baseline) / baseline] x 100). Both parameters represent the most used parameters of the PORH test, and have excellent reproducibility [15,23,24].

### 2.4. Statistical analysis

A power analysis was performed to estimate the sample size required to test the primary objective hypothesis regarding the correlation between maternal skin microvascular parameters and first trimester PlGF levels. Considering a Fisher Z-transformation method for estimating Pearson's correlation distribution, an expected correlation of 0.45, a null correlation of 0.00, and a type I error of 0.05, a sample size of 47 patients was required to achieve a power of 0.8.

The continuous variables were presented by mean ± standard deviation (SD) or median and interquartile ranges (IQR), according to Shapiro-Wilk test for normality.

In order to evaluate the association between continuous variables the Pearson's correlation coefficient and its 95 % confidence interval (CI) was used.

To assess the difference between groups in continuous variables the *t*-test, Satterthwaite *t*-test or Mann Whitney test were used according to Shapiro-Wilk and F-test for normality and homoscedasticity results. The significant level was set to 5 %.

## 3. Results

Fifty-three pregnant women were enrolled and signed an informed consent. Among the 53 women, two chose not to perform the preeclampsia screening and had only free β-hCG and PAPP-A levels assessed. The remaining 51 women performed the combined preeclampsia and aneuploidy screening and were assessed for all markers mentioned above.

Maternal characteristics and pregnancy outcomes are illustrated in Table 1.

The results of the correlations analyses between the post-occlusive hyperemic response parameters and the serum biochemicals and biophysical markers are illustrated in Table 2, Figs. 2 and 3. Table 3 shows the comparisons of the microvascular parameters between categories of serum biomarker levels (above and below the median).

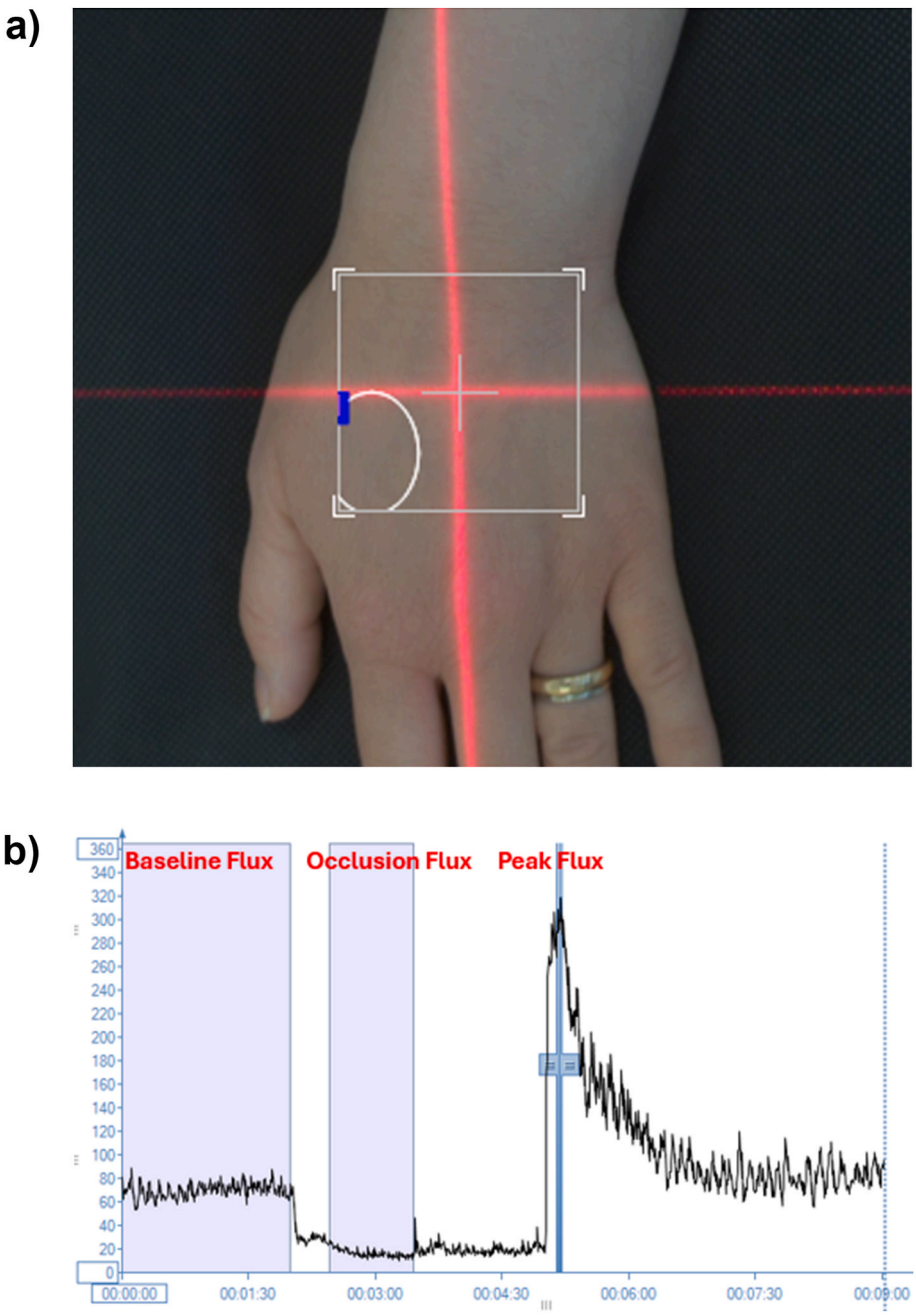


**Fig. 1. A:** Microvascular skin blood flow at the dorsal face of the hand assessed with LSCI; **B:** example of a record of the skin blood flow using LSCI coupled with PORH.

As shown in Fig. 2, there was a moderate positive correlation between PlGF MoM and the base-to-peak flux (r = 0.51, 95 % CI 0.27–0.69), indicating that higher concentrations of PlGF were associated with a higher post-occlusive reactive hyperemic response. PlGF MoM also presented a weak, yet significant, positive correlation with the absolute value of peak flux (r = 0.31, 95 % CI 0.04–0.54, Table 2).

The association between MoM above the median and increased base-to-peak flux almost reached statistical significance, when compared to MoM below median (251.3 % versus 220 %, p 0.07, Table 3).

A correlation with the parameters of the hyperemic response was also found for the other two first-trimester maternal serum biomarkers. In particular, PAPP-A MoM levels above the median were associated with higher base-to-peak flux compared to levels below the median (253.41 % versus 215.08 %, p = 0.02, Table 3). Additionally, PAPP-A levels showed a weak positive correlation with the base-to-peak flux (r = 0.32, 95 % CI 0.05–0.54).

Free β-hCG levels showed a moderate positive correlation with the peak flux (r = 0.4, 95 % CI 0.15–0.60, Fig. 3) and a weak but statistically significant correlation with the base-to-peak flux (r = 0.35, 95 % CI 0.08–0.56). A higher base-to-peak flux was observed in cases where free β-hCG MoMs were above the median (263.1 % versus 220 %, p = 0.015), compared to lower levels of free β-hCG (Table 3).

No association was found between the parameters of the post-occlusive hyperemic response and the maternal biophysical markers (Table 2). Specifically, there was no significant correlation with uterine artery doppler results, expressed either as PI, PI MoM or percentiles. Maternal MAP was not correlated with the parameters of the test.

**Table 1**
Maternal characteristics and pregnancy outcomes.

| | |
|---|---|
| Maternal age (years) | 35.9 ± 4.6 |
| Body mass index (kg/m2) | 22 (20.8, 24.7) |
| Nulliparity | 32/53 (60.4 %) |
| Assisted reproductive technologies | 10/53 (18.9 %) |
| Gestational age during microvascular function assessment (weeks) | 12.53 ± 0.48 |
| Gestational diabetes mellitus | 13/53 (24.5 %) |
| Hypertensive disorders | 1/53 (1.9 %) |
| Fetal growth restriction | 1/53 (1.9 %) |
| Method of delivery: Spontaneous vaginal delivery | 34/53 (64.15 %) |
| Operative vaginal delivery | 4/53 (7.55 %) |
| Cesarean Section | 15/53 (28.3 %) |
| Gestational age at delivery | 39.43 (38.57, 40.21) |
| Birthweight (g) | 3421.6 ± 402.67 |
| Birthweight centile | 48 (23, 68) |
| Fetal gender: Male | 23/53 (43.4 %) |
| Female | 30/53 (56.6 %) |

Data are expressed as n (%) and mean ± SD or median (25th −75th IQR) based on their distribution.

**Table 2**
Results of the correlation analyses between the parameters of hyperemic response and maternal serum biochemical and biophysical marker (continuous variables).

| | Marker | Pearson's CC | 95 % Confidence Interval |
|---|---|---|---|
| **Base-to-peak flux (%)** | PlGF (MoM) | **0.51** | **0.27-0.69** |
| | PAPP-A (MoM) | **0.32** | **0.05-0.54** |
| | Free β-hCG (MoM) | **0.35** | **0.08-0.56** |
| | Uterine artery Pulsatile Index | 0.15 | −0.14-0.42 |
| | Uterine artery Pulsatile Index Percentile | 0.13 | −0.15-0.39 |
| | Uterine artery Pulsatile Index (MoM) | 0.13 | −0.15-0.39 |
| | Mean Arterial pressure | −0.10 | −0.36-0.17 |
| **Peak flux (Perfusion units)** | PlGF (MoM) | **0.31** | **0.04-0.54** |
| | PAPP-A (MoM) | 0.22 | −0.05-0.47 |
| | Free β-hCG (MoM) | **0.40** | **0.14-0.60** |
| | Uterine artery Pulsatile Index | 0.24 | −0.03-0.49 |
| | Uterine artery Pulsatile Index Percentile | 0.20 | −0.09-0.46 |
| | Uterine artery Pulsatile Index (MoM) | 0.25 | −0.02-0.50 |
| | Mean Arterial pressure | −0.09 | −0.35-0.18 |

Free beta-hCG, PAPP-A and MAP were assessed in 53 patients, PlGF was assessed in 51 patients, uterine artery PI was assessed in 52 patients.

## 4. Discussion

This cross-sectional study demonstrates that first trimester PlGF levels positively correlate with maternal skin microvascular reactivity parameters, assessed by LSCI coupled with PORH. These parameters were also positively correlated with the other first trimester serum biochemical markers, PAPP-A and free β-hCG, although the strongest association was observed with PlGF.

A decreased placental production of PlGF is considered a marker of syncytiotrophoblast stress and poor placentation [25]. A lower post-occlusive reactive hyperemic response (expressed either as the lower absolute peak flux value or a lower increase in relation to baseline after occlusion release) indicates impaired microvascular function and has been associated with cardiovascular diseases [14,26,27]. Our results indicates that a better microvascular endothelial function is associated with higher concentrations of PlGF levels, which reflect placental function, suggesting that maternal peripheral microvascular function may mirror placental microcirculation development.

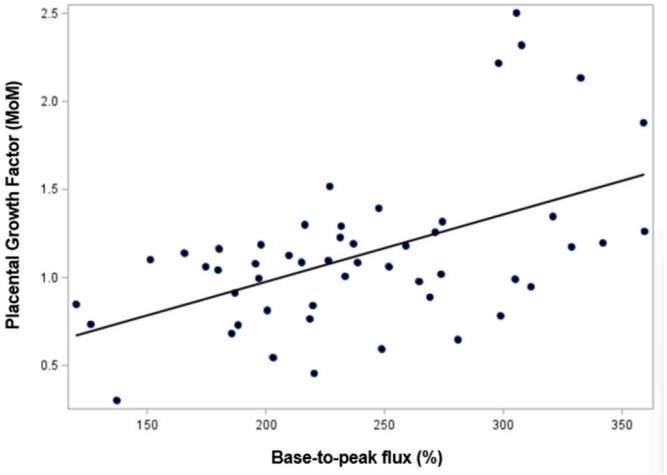


**Fig. 2.** Correlation between Placental growth factor (MoM) and base-to-peak flux.

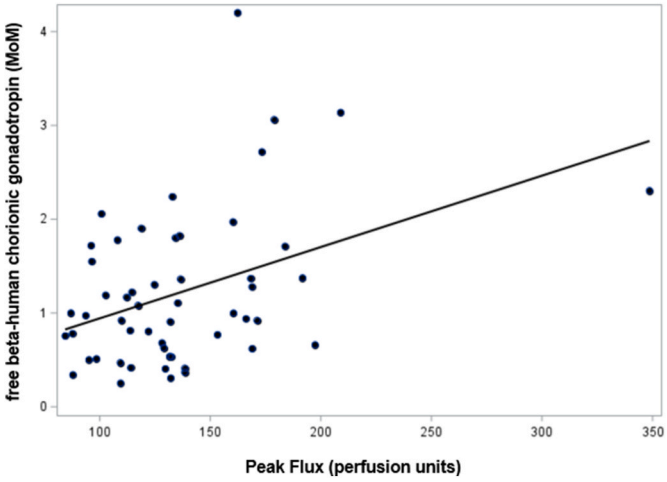


**Fig. 3.** Correlation between free beta-human chorionic gonadotropin (MoM) and peak flux.

The correlation between the post occlusive reactive hyperemic response and PAPP-A and free β-hCG levels can be explained by a similar mechanism. Decreased levels of these biomarkers have been attributed to altered placental function, which determines a reduced synthesis and secretion of placental products [28]. Moreover, first trimester low PAPP-A levels are associated with poor pregnancy outcomes, such as miscarriage, hypertensive disorders, FGR and stillbirth [28–33]. Although the free β-hCG is not used for preeclampsia risk assessment, low levels of this biomarker in the first trimester have also been associated with some adverse outcomes, including pregnancy loss and FGR [29–31,33].

In our study, no correlation was found between maternal biophysical markers (uterine artery Doppler and MAP) and microvascular reactivity. The lack of correlation with MAP may be explained by the small variability in this measurement. The absence of correlation with the uterine artery PI may be due to the fact that, while increased resistance in these vessels reflects inadequate trophoblastic invasion, abnormal skin microcirculatory function may indicate systemic vascular abnormalities predisposing to preeclampsia, independently of uterine artery impedance. Indeed, uterine artery Doppler is often used in combination with other biomarkers to enhance its sensitivity. Interestingly, Antonios et al. have shown that assessing skin microcirculation using capillaroscopy in

**Table 3**
Comparisons of the parameters of hyperemic response between categories of maternal serum biochemical marker levels (above and below the median).

| | Marker | Number | Mean ± SD | Median (1,3 IQR) | P value |
|---|---|---|---|---|---|
| **Base-to-peak flux (%)** | PlGF < median | 19 | 220.0 ± 58.1 | 218.4 (187.0, 269.1) | 0.07 |
| | PlGF > median | 32 | 251.3 ± 58.2 | 237.6 (212.3, 301.6) | |
| | PAPP-A < median | 20 | 215.1 ± 55.3 | 214.0 (181.5, 256.5) | **0.02** |
| | PAPP-A > median | 33 | 253.4 ± 57.3 | 236.8 (215.0, 304.8) | |
| | Free β-hCG < median | 26 | 219.1 ± 52.6 | 220.0 (187.0, 248.6) | **0.015** |
| | Free β-hCG > median | 27 | 258.1 ± 59.5 | 263.1 (209.6, 307.5) | |
| **Peak flux (Perfusion units)** | PlGF < median | 19 | 126.1 ± 26.9 | 124.7 (109.3, 138.5) | 0.11 |
| | PlGF > median | 32 | 143.9 ± 50.2 | 132.6 (113.3, 166.7) | |
| | PAPP-A < median | 20 | 124.3 ± 23.4 | 123.4 (109.4, 136.8) | 0.06 |
| | PAPP-A > median | 33 | 143.8 ± 50.5 | 132.4 (109.8, 168.9) | |
| | Free β-hCG < median | 26 | 125.9 ± 28.5 | 128.6 (109.3, 138.4) | 0.08 |
| | Free β-hCG > median | 27 | 146.6 ± 52.1 | 135.2 (112.1, 168.8) | |

Free beta-hCG and PAPP-A were assessed in 53 patients, PlGF was assessed in 51 patients.

pregnancy can increase the sensitivity of uterine artery doppler in predicting preeclampsia from 0.57 to 0.86 [34].

To our knowledge, this study is the first to demonstrate that maternal skin endothelial microvascular function in the first trimester correlates with placental microcirculation development, assessed indirectly by PlGF levels.

Savviduo et al. found no correlation between second-trimester alterations in PlGF levels and endothelial dysfunction, assessed by flow-mediated dilatation of the brachial artery diameter [35]. However, second trimester PlGF levels alone have lower predictive performance for preeclampsia, and the sFLt-1/PlGF ratio is more frequently used to increase pooled sensitivity and specificity [9].

Very few have assessed the correlation between systemic endothelial function and the first-trimester placental circulation. In line with our findings, Iacobaeus et al. found a positive correlation between first trimester PAPP-A levels and skin microvascular flux parameters, assess by laser doppler perfusion imaging coupled with iontophoresis. The authors suggest that reduced endothelium-dependent skin microvascular reactivity is a possible early marker of impaired placentation and pregnancy complications [17].

Furthermore, the same group have demonstrated that first trimester maternal vascular dilatation capacity, assessed in the brachial artery and in the skin microcirculation, was positively associated with neonatal birthweight. These results further support the hypothesis that first trimester maternal endothelial function reflects the state of the utero-placental unit [11].

A previous study conducted by our group demonstrated that microvascular reactivity, assessed by LSCI coupled with PORH, improves from the first to the third trimester of pregnancy. Additionally, that study provided evidence of enhanced microvascular reactivity as early as the first trimester of pregnancy, compared to non-pregnant controls [36].

The present study suggests that assessing microvascular endothelial function in the first trimester could provide valuable information about the risk of placental-related disorders. Indeed, reduced microvascular reactivity could potentially serve as a marker of impaired placental invasion and, therefore, as an early predictor of pregnancy complications. This hypothesis is supported by evidence indicating that changes in microvascular reactivity and endothelial dysfunction precede the onset of preeclampsia by weeks or months [37]. The predictive value of first trimester assessment of microvascular reactivity, therefore, warrants further investigation in large prospective cohort studies and in complicated pregnancies.

The development of preeclampsia and FGR is believed to result from impaired placentation due to inadequate trophoblastic invasion, and from abnormalities in early placental angiogenesis [2,7,29]. Preeclampsia and FGR appear to arise from a maternal predisposition to endothelial dysfunction, which contributes to shallow placental implantation, potentially leading to increased risks of maternal cardiovascular disease later in life [38].

On the other hand, it has been suggested that PlGF plays a crucial role in cardiovascular remodelling in pregnancy [39]. Low concentrations of PlGF are associated with increased risk of cardiovascular dysfunction later in life, even in uncomplicated pregnancies [3]. In mouse model, the expression of PlGF has been linked to systemic maternal cardiovascular adaptations to pregnancy, with high levels of PlGF in mid-gestation providing protective functions for the maternal cardiovascular system [40].

Whether endothelial microvascular dysfunction is the cause or the consequence of impaired placentation and low PlGF levels remains an area that requires further exploration. Understanding the microcirculation in pregnant women is crucial to shedding light on this issue.

The skin microvascular flow assessment through LSCI coupled with PORH provides an overall index of microvascular function [15] and offers an opportunity to instigate endothelial dysfunction associated with pregnancy complications and to understand the mechanisms that influence fetal growth. The availability of this non-invasive, novel technique may in the future prove to be a valuable adjunctive tool for the prediction and diagnosis of such diseases.

There are several strengths of the present study. We used a novel, non-invasive, technique to assess skin microcirculation *in vivo*. PORH is broadly used test for the non-invasive assessment of peripheral microvascular function with well-established validity and is highly reproducible when combined with LSCI [14,24].

Other strengths include the study design, the accurate selection of eligible patients, and the fact that all registrations were performed in a single center and in a controlled environment by trained physicians, according to a standardized protocol.

Certain limitations concerning the LSCI technique should be acknowledged. The Laser technique does not directly measure skin blood flow but rather provides an index of skin perfusion quantified as the product of average red blood cell velocity and their concentration, often referred to as flux [15]. Therefore, results are expressed in arbitrary perfusion units and not in absolute units (i.e., ml/min). However, we also calculated the base-to-peak flux which is the relative increase compared to baseline.

In conclusion, first-trimester skin microvascular reactivity, assessed by LSCI coupled with PORH, is positively associated with serum placental biomarkers levels, in particular PlGF. These novel findings suggest that maternal peripheral microvascular function may reflect the placental microcirculation. Further studies investigating pregnancies complicated by placental-related diseases are warranted to determine whether this tool could serve as an early marker of placental function.

## CRediT authorship contribution statement

**Mor Huri:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Isabella Abati:** Data curation. **Chiara Bartolini:** Data curation. **Alessia Piacenza:** Data curation. **Lorenzo Tofani:** Formal analysis. **Arianna Vallario:** Data curation. **Mariarosaria Di Tommaso:** Visualization, Validation, Supervision, Project administration, Conceptualization. **Viola Seravalli:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Investigation, Conceptualization.

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## Declaration of competing interest

The authors do not have conflicts of interest to disclose.

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