Circulating angiogenic profiles and histo-morphological placental characteristics of uncomplicated post-date pregnancies

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\textbf{ABSTRACT}

\textbf{Introduction:} The objectives of this study were to describe the histo-morphology of post-date placentas in clinically uncomplicated pregnancies without adverse delivery outcomes and the association with maternal circulating pre-delivery Placental Growth Factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), as well as the sFlt-1/PlGF ratio.

\textbf{Methods:} Post-date placentas (gestational week $\geq 40^{+2}$, $n = 87$) were macroscopically and histo-morphologically assessed according to the international, standardized Amsterdam Workshop Consensus Group criteria. Inter-rater agreement was evaluated by percentage of agreement. PlGF and sFlt-1 concentrations were available from maternal serum sampled close to delivery, and were compared by Mann-Whitney $U$ test. Linear regression analyses were adjusted for predefined potential confounders.

\textbf{Results:} The majority of the post-date placentas showed morphological signs of delayed maturation. About half of the placentas showed increased syncytial knotting and fibrin. In placentas with increased presence of intervillous fibrin, median maternal PlGF level was significantly lower ($p = 0.004$), median sFlt-1 level higher and sFlt-1/PlGF ratio significantly higher ($p = 0.002$) compared to those with normal fibrin amounts. Increased placental syncytial knotting was associated with lower levels of PlGF, higher sFlt-1 and higher sFlt-1/PlGF ratio compared to those with normal knotting.

\textbf{Discussion:} Our standardized morphological study of post-date placentas in clinically healthy women with uncomplicated pregnancies and delivery outcomes revealed delayed maturation in the majority of placentas. Increased pre-delivery circulating anti-angiogenic profile was associated with increased intervillous fibrin and syncytial knotting. We propose that circulating maternal angiogenic biomarkers may be of future use in clinical post-date pregnancy assessment, as they reflect important aspects of placental health and function.

1. Introduction

Optimal placental function is central for fetal development and growth, as well as for maternal well-being during pregnancy. Post-date pregnancies have an increased risk of stillbirth [1] and neonatal morbidity [2], likely due to placental aging [1,3] and increased cellular syncytiotrophoblast stress through multiple pathways [4]. Targeting of post-date pregnancies at highest risk for adverse outcome would be helpful in clinical management.

Imbalances in maternal circulating placenta-associated biomarkers, such as soluble fms-like tyrosine kinase-1 (sFlt-1) and Placental Growth Factor (PIGF), are associated with placenta-related pregnancy complications, particularly pre eclampsia and fetal growth restriction, or a combination of the two [5–7]. We have previously proposed that low PIGF and high sFlt-1 may be used as general markers for syncytiotrophoblast stress [4] and thus as markers of placental health and reserve capacity [8]. In line with our hypothesis, we found signs of increased placental stress in post-date pregnancies compared to term pregnancies [8], reflected by a trend towards lower PIGF values and significantly higher sFlt-1 and sFlt-1/PIGF values. In support of a wider
utility of these biomarkers, a large study concluded that a low pro-angiogenic (PIGF/sFlt-1) ratio correlated with a high burden of placental maternal vascular malperfusion signs, in prematurely delivered pregnancies before gestational week (GW) 34 [9]. Another recent study reported an association between low first-trimester levels of PIGF and the presence of maternal vascular malperfusion, indicating placental insufficiency and thus an increased risk of development of placental syndromes [10].

Normal villous maturation is essential for optimal placental function and fetal demands of oxygen and nutrition [11]. Ramification and maturation from predominating immature intermediate villi in the first and second trimester to the mature intermediate and terminal villi in the end of third trimester reflect a dynamic maturation process [11]. Placentas age at different speeds, following multiple and likely heterogeneous biochemical pathways [12], possible due to a combination of genetic predisposition [13] and external exposure [12]. The risk of stillbirth rises after GW 39, with a marked increase after GW 40 [14]. It has previously been described that post-date placentas (GW > 41) undergo an aging process, involving oxidative damage to DNA, RNA and lipids similar to what is seen in placentas from stillbirths [1]. An older study, including 8 term and 15 post-date (GW > 42) placentas, showed increased syncytiotrophoblastic degeneration and intervillous fibrin deposition in post-date placentas compared to term placentas of healthy pregnancies [15]. The authors interpreted these histological findings as signs of decreased placental activity [15].

The aim of the present study was firstly to describe the histomorphology of placentas in post-date pregnancies that remained clinically uncomplicated throughout pregnancy and delivery. Secondly, we investigated the association between the placental histomorphology of these post-date placentas and maternal circulating pre-delivery PIGF, sFlt-1, and the calculated sFlt-1/PIGF ratio.

2. Methods

2.1. Recruitment of pregnant women

Placentas from 87 post-date (GW ≥ 40\textsuperscript{+2}) singleton pregnancies were collected prospectively from women who had been recruited at routine post-date evaluation or at admission for induction of labor at Oslo University Hospital. Post-date evaluation is routinely done between GW 41\textsuperscript{+2}–41\textsuperscript{+4}, but one week earlier for women ≥40 years [16]. The present study is a sub-study of the ongoing “PREDelivery Placental biomarkers - Pregnancy and Delivery outcome (PREPPeD) Study” (NCT03100088) [8]. Women were included to the study from September 2016 to December 2017 and gave informed written consent.

As described in detail elsewhere [8], 426 of the first 501 recruited women had uncomplicated post-date pregnancies without adverse pregnancy, delivery or neonatal outcomes. These 426 women provided blood samples taken prior to delivery for the construction of previously published novel post-date PIGF and sFlt-1 reference ranges, as shown in Fig. 1 [8]. As part of the PREPPeD study, every fifth placenta was collected for later evaluation, resulting in 91 available placentas for the present study. All pregnancy outcomes were reviewed by our Diagnostic Advisory Group, consisting of two senior consultant obstetricians not affiliated to the study and blinded for PIGF and sFlt-1 results. The reviewing process is in detail described elsewhere [8]. In short, all medical journals from the women and their neonates, including placental histology, were reviewed. The Diagnostic Advisory Group then concluded whether there was an adverse outcome (Supplemental Table 1 [17]) and whether this outcome most likely was due to placental dysfunction [8]. As a result, only post-date pregnancies with apparently well-functioning placentas were included in the final cohort contributing to the present study. Of the 91 included placentas, four were excluded: three had no available tissue sections slides for evaluation and one stemmed from a vanishing twin pregnancy, resulting in 87 placentas available for evaluation (Fig. 1). No pregnancies with fetal structural/chromosomal abnormalities were included. None of the included pregnancies resulted in a baby small for gestational age (SGA); as defined by a birthweight < 10th centile.

Following delivery, the placentas were weighed with the umbilical cord, membranes and amniotic fluid/blood by the midwife within 30 min. The placentas were then sent dry to the Department of Pathology, without any fluid of fixation or conservation, for further processing at the Oslo University Hospital, Ullevål, Department of Pathology.

2.2. Placental pathologic assessment

The 87 placentas were formalin-fixed (4% buffered) for a minimum of 48 h, before macroscopic and microscopic examination was conducted, according to Amsterdam Workshop Consensus Criteria [18]. Placental net weight was documented, after removal of cord and membranes, as were three-dimensional measurements of the disc, umbilical cord insertion, length and diameter and vessel number. The placental discs were cut into approximately 1 cm thick slices; the slices were then inspected for thrombotic lesions, infarcts, bleeding or other lesions. Each lesion was described three-dimensionally with its location and size. Sample sections were taken from the umbilical cord, both fetus-near and insertion-near, membrane roll, and full-thickness tissue sections were taken from lesions and macroscopically normal looking tissue. All sampling was assessed from the inner disc, with minimum 2.5 cm distance from the peripheral disc border. Samples were further processed in small blocks, embedded in paraffin, and approximately 3.5 μm thick sections were stained with Hematoxylin Eosin (HE).

All placenta sections were examined according to Amsterdam Workshop Consensus Criteria [18], using standardized criteria to evaluate decidual vasculopathy [19], increased placental villous syncytial knotting [18,20], villous maturation [18,21], chorangiosis [11,22], chorangiomiomatosis [23], plasma cell deciduitis [24], and acute
chorioamnionitis [24] (Supplemental Table 2 [25]). In addition to these criteria, morphological criteria by Turowski and Vogel [11] were added for detailed evaluation of placenta villous maturation disorders. Maternal vascular malperfusion was defined as the presence of increased intervillous fibrin deposits, increased syncytial knotting, villous infarction or distal villous hypoplasia according to gestational age references [26]. Delayed villous maturation was used to denote reduced fetal vessel number in the chorionic villi, with missing differentiation into vasculosyncytial membranes [18]. In case of findings not compatible with the predefined criteria of placental (villous) maturation, the criterion with the closest resemblance to the overall morphological appearance was chosen. All slides were examined by an obstetric resident (investigator A: BMM), trained in using the predefined placental histo-morphological criteria and an experienced perinatal pathologist (investigator B: GT). In case of disagreement between the observers, results from the perinatal pathologist (investigator B) were used in the statistical analyses. Both investigators were blinded for maternal and fetal characteristics as well as pregnancy and delivery outcome, but were aware of gestational age at delivery.

### 2.3. Immunohistochemistry

Immunohistochemistry staining of CD15 was done on a Ventana BenchMark ULTRA machine using OptiView DAB IHC detection kit. The slides were deparaffinized and incubated with primary antibody (CD15 mouse monoclonal antibody from DAKO, clone Carb-3), counterstained with Hematoxylin II, and washed with EZ-Prep solution followed by rinsing in tap water. The slides were then dehydrated through graded alcohols and cleaned in xylene base before beingcoverslipped on a DAKO automated coverslipper using PERTEX.

The immunohistochemical reaction was assessed in the chorionic plate and in the vessels of the villi. The staining reaction was evaluated according to the grading system described by Seidmann et al. [27], by the same blinded investigators as above (A and B).

### 2.4. Blood sampling and analysis

The maternal PIGF and sFlt-1 serum concentrations were quantified jointly for the cohort postpartum, blinded for clinical information, at the Department of Medical Biochemistry, Oslo University Hospital, on a cobas e 801, using the fully automated Elecsys®® PIGF and sFlt-1 system, according to the manufacturer’s instructions. All concentrations were within the measuring ranges of the PIGF and sFlt-1 assays (3–10,000 pg/ml and 10–85,000 pg/ml, respectively). The coefficients of variation were ≤2.1% for PIGF and ≤1.8% for sFlt-1.

### 2.5. Statistical analysis

The biomarker data were not normally distributed and thus medians were compared by Mann-Whitney U test. Categorical variables were compared by Chi-square test. Statistical significance was considered as p ≤ 0.05. Percentage of agreement was calculated to evaluate interrater agreement for each of the predefined histologic criteria (summarized in Table 2). The percentage of agreement is calculated as the number of agreements divided by the total number of units of observation that are rated, multiplied by 100 [28]. A percentage of agreement >75% is considered acceptable [29]. Linear regression was performed, adjusted for predefined confounders. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

### 3. Results

The maternal, macroscopic placental and biomarker characteristics are shown in Table 1. Maternal clinical characteristics were comparable between the included women in the main PREPcED study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years), mean</td>
<td>41.5 (6.4)</td>
</tr>
<tr>
<td>Gestational age (weeks), mean</td>
<td>39.2 (2.2)</td>
</tr>
<tr>
<td>Birth weight (grams), mean</td>
<td>3380 (532)</td>
</tr>
<tr>
<td>Placental net weight (grams), mean</td>
<td>621 (117)</td>
</tr>
<tr>
<td>BMI at delivery, 5 umbilical artery PI.</td>
<td>3.7 (0.9)</td>
</tr>
<tr>
<td>Male</td>
<td>42 (48.3)</td>
</tr>
<tr>
<td>Female</td>
<td>45 (51.7)</td>
</tr>
<tr>
<td>Umbilical artery PI, mean</td>
<td>7.1 (1.2)</td>
</tr>
<tr>
<td>Serum angiogenic biomarkers, median (25–75%)</td>
<td>sFlt-1 (pg/mL) 4298 (2908–5577) sFlt-1/PIGF ratio 25.6 (12.9–42.1)</td>
</tr>
</tbody>
</table>

BMI: body mass index, PI: pulsatility index, PIGF: placental growth factor, SD: standard deviation, sFlt-1: soluble fms-like tyrosine kinase-1. Missing data, 1 BMI at delivery, 5 umbilical artery PI.

(38x146)agreement were compared by Mann-Whitney performed, adjusted for predefined confounders. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.
morphologically (Percentage of agreement ranging from 64 to 100 depending on histological criterion examined). Fig. 2 A-E shows pictures of the typical morphological findings in placentas diagnosed with distal villous hypoplasia, increased syncytial knotting, increased intervillous fibrin, acute chorioamnionitis and delayed maturation.

The majority (77%) of the placentas had signs of delayed maturation (Table 2), with a significantly larger proportion among the pregnancies with vaginal deliveries compared to the ones with acute cesarean section (82% vs. 53%, p = 0.017) (Supplemental Table 5).

Immunostaining did not show increased CD15-expression in the endothelial and stromal cells, as evaluated according to the grading system described by Seidmann et al. [27] (Supplemental Table 6).

Increased syncytial knotting was present in 56%, increased intervillous fibrin depositions in 45%, and histological signs of acute chorioamnionitis in 49% (Table 2), without any apparent association with delivery mode (Supplemental Table 4).

In median, the blood samples for angiogenic marker analyses were taken two days prior to delivery, and 40% were taken on the day of delivery or the day before. Increasing maternal levels of both circulating PlGF and sFlt-1 protein, and lower sFlt-1/PlGF ratio, correlated with increasing placental weight (Supplemental Table 6). After linear regression with adjustment for maternal age, parity, gestational age at delivery, smoking, maternal body mass index at delivery, sex and newborn weight, only sFlt-1 maintained a significant positive correlation with placental weight (p = 0.005) (Supplemental Table 7). There was a positive correlation of placental weight with birth weight of the neonate (p < 0.001) and maternal age (p = 0.038), after adjustments (Supplemental Table 7).

Maternal vascular malperfusion was present in 79% of the placentas. The distributions of the individual criteria contributing to the maternal vascular malperfusion diagnosis are listed in Table 2. In placentas with maternal vascular malperfusion, we observed a tendency towards lower median maternal circulating PlGF (185 vs 242 pg/mL, p = 0.178) and higher sFlt-1 levels (4402 vs 3979 pg/mL, p = 0.908) as well as sFlt-1/PlGF ratio (26.4 vs 20.3, p = 0.340), compared to the placentas without, although not statistically significant (Table 3).

When comparing the individual histological criteria to the median values of the placenta-associated biomarkers from maternal circulation taken prior to delivery, placentas with increased intervillous fibrin had significantly lower median level of PlGF (156 vs 228 pg/mL, p = 0.004),
and significantly higher median level of sFlt-1 (3817 pg/mL, p = 0.094) compared to the ones without increased intervillous fibrin (Fig. 3 and Table 3). Although not statistically significant, we also observed higher median level of sFlt-1 (4763 vs 4001 pg/mL, p = 0.094) in placentas with signs of increased intervillous fibrin compared to the ones without.

For the group of placentas with signs of increased syncytiot knotting, we also found non-significant lower median level of PI GF (179 vs 193 pg/mL, p = 0.360) and higher median level of sFlt-1 (4420 vs 3755 pg/mL, p = 0.088) and sFlt-1/PI GF ratio (26.5 vs 23.7, p = 0.313) (Fig. 3 and Table 3) compared to the ones without villous infarction.

Interestingly, in the group of placentas with distal villous hypoplasia, we observed significantly higher median values of PI GF (243 vs 185 pg/mL, p = 0.050), and significantly lower median values of sFlt-1 (2190 vs 4430 pg/mL, p = 0.001) and sFlt-1/PI GF ratio (8.4 vs 28.9, p = 0.001) compared to the ones without (Fig. 3 and Table 3).

Placentas with histological signs of acute chorioamnionitis (49%) had a significantly longer duration of labor compared to those without histological signs of acute chorioamnionitis (median 11 h, 6 min. vs. 6 h, 36 min, p = 0.002). Three patients had clinical signs of chorioamnionitis (3.4%), which were confirmed by placental histology. All three delivered by caesarian section due to prolonged first stage of labor and clinical signs of chorioamnionitis. No correlation was found between placental signs of acute chorioamnionitis and altered placenta-associated biomarker levels.

4. Discussion

4.1. Main finding

To the best of our knowledge, this is the first extensive description of post-date placentas from clinically healthy women with uncomplicated pregnancies without adverse outcomes using predefined and standardized histo-morphological criteria [18]. In our study of 87 post-date placentas, maternal vascular malperfusion was seen as increased intervillous fibrin deposition, increased syncytiot knotting, villous infarction or distal villous hypoplasia, correlating with a trend towards increased antiangiogenic biomarker profile in maternal circulation, indicating increased placental cellular stress [4]. This antiangiogenic pattern of low PI GF, high sFlt-1 and sFlt-1/PI GF ratio is in line with what is seen in several obstetric syndrome pregnancies associated with placental dysfunction, such as early-onset preeclampsia and early-onset fetal growth restriction [4].

In this healthy post-date cohort without adverse delivery outcomes, 77% of the placentas showed signs of delayed villous maturation, microscopically seen as reduced fetal vessel number in the chorionic villi, with missing differentiation into vasculosyncytial membranes [18]. Delayed villous maturation has previously been associated with maternal obesity and metabolic disorders, intrauterine hypoxia, fetal growth restriction and fetal death [30]. In our study of post-date placentas, we only included healthy, normotensive, euglycemic women with a BMI <30 kg/m² and a live born, appropriate for gestational age baby without congenital anomalies or adverse delivery outcome. The presence of villous maturation disorders in our cohort should therefore not be influenced by any of these risk factors. Increased CD15-expression in the macro- and microvascular endothelium has previously been described to represent a marker of pathological villous immaturity at term associated with fetal growth restriction, fetal death, fetal acidosis, preeclampsia, Parvovirus B-19 infection and gestational diabetes mellitus [27]. Possibly, our inclusion of only clinically healthy post-date pregnancies without adverse delivery outcomes might explain why we did not find an increased CD15-expression in our cohort. This may suggest that CD15-expression may represent a good marker for pathological villous immaturity in term pregnancies with adverse delivery outcomes, but possibly not be a marker of delayed villous maturation per se.

The relatively high proportion of delayed villous maturation in our study may possibly explain why these pregnancies have been able to progress beyond due date and still provide a healthy environment for the fetus. However, delayed villous maturation is commonly seen in stillbirths caused by acute placental dysfunction in the third trimester [31], suggesting that some placentas are able to compensate for insufficient...
Fig. 3. Comparison of median values of placental growth factor (PlGF; A,D,G), soluble fms-like tyrosine kinase-1 (sFlt-1; B, E, H) and sFlt-1/PlGF ratio (C, F, I) in post-date placentas according to morphological evidence of increased fibrin and syncytial knotting and presence of distal villous hypoplasia. Circles represent placental biomarker values in the group of placentas without signs of increased fibrin, syncytial knotting and distal villous hypoplasia. Squares represent placental biomarker values in the group of placentas with signs of increased fibrin, syncytial knotting and presence of distal villous hypoplasia. The bars demonstrate median values with 95% confidence interval. Significant difference ($p \leq 0.05$) is marked by an asterisk.*
developmental and/or differentiation defects whereas others cannot. At present, there exists no safe method to prenatally identify these placentas with higher risk of acute dysfunction and thus risk for adverse neonatal outcome, other than assessing fetal well-being by cardioangiography and ultrasound biophysical profile [32,33]. Our novel finding of correlation between placental maturation disorders and antiangiogenic biomarker profile may be developed further into a tool assisting in identifying pregnancies with higher risk of acute placental dysfunction.

Our finding of increased syncytial knotting in half of the studied post-date placentas is comparable with previous reports of increasing presence of syncyial knots with increasing gestational age [20]. The finding of increased syncytial knotting relative to gestational age is thought to be a diagnostic indicator of uteroplacental malperfusion [34] and placental ischemia [35]. In our cohort, increased syncytial knotting and fibrin did not correlate with the mode of delivery. All women underwent active labor, and thus, all placentas were exposed to the increased stress of uterine contractions. The influence of uterine contraction on the formation of syncyial knots could therefore not be evaluated.

In about half of the post-date placentas we found signs of increased intervillous fibrin depositions. This is a much larger proportion than the 6.4% previously reported from uncomplicated term pregnancies [36], but closer to the 39.1% reported from term pregnancies in older women [37]. Fibrin deposition is a sign of reduced maternal circulation [34], and might suggest that increased placental cellular stress is of the same etiology in post term placentas as in placentas from older pregnant women.

The facts that we found dysregulated placenta-associated biomarkers, namely lower PlGF and higher sFlt-1 and sFlt-1/PlGF ratio, in placentas with increased fibrin compared to the ones without, supports our hypothesis of increased placental cellular stress in uncomplicated post-date pregnancies [8]. The association between dysregulated placental biomarkers and increased intervillous fibrin has previously been demonstrated in fetal growth restriction and fetal demise [38], as well as in late-onset preeclampsia [26]. The correlation between increased intervillous fibrin, as a sign of maternal vascular malperfusion, and dysregulated placenta-derived biomarkers is in line with increasing placental malperfusion due to villous congestion [4] and reduced placental capacity towards the end of pregnancy. This is also in line with reports describing a correlation between altered placental biomarkers and maternal vascular malperfusion lesions [39]. A correlation between late-onset preeclampsia, altered placental biomarkers (especially low PlGF) and placental histological findings consistent with maternal vascular malperfusion has also been described [26]. This parallels to our findings of lower PlGF in healthy, uncomplicated post-date pregnancies, and might be indicative of the increased tissue and cellular stress the placenta undergoes when the pregnancy proceeds past term. We suggest that our novel finding of correlation between increased fibrin and antiangiogenic biomarker profile may be developed further into a tool assisting in identifying pregnancies with potentially lower placental capacity post-date due to increased cellular stress.

Increased amounts of syncyial knots, intervillous fibrin and distal villous hypoplasia are criteria for the diagnosis of maternal vascular malperfusion and are often interpreted as signs of accelerated maturation [18]. Delayed maturation is a feature not based on this set of criteria, but rather on features of reduced fetal vessel number in the chorionic villi with missing differentiation into vasculosyncytial membranes and stromal and trophoblast maturation defects [11], and defines a maturation delay for gestational age [40–45]. Today, the criteria for maternal vascular malperfusion are subjective and therefore challenge reproducibility, thus the findings of increased syncyial knots and intervillous fibrin might be over- or under-diagnosed. This highlights the need for future studies to develop better and more standardized biological criteria for evaluation of the normal amount of syncyial knots and intervillous fibrin according to gestational age, as this has been showed to be difficult even in earlier studies [46,47].

Histopathological signs of chorioamnionitis at term have previously been suggested to represent a “sterile inflammation” [48] associated with labor and/or prolonged rupture of membranes [49], rather than a clinical infection. The histopathological signs of chorioamnionitis can therefore not be expected to be associated with placenta-associated biomarkers measured in blood taken prior to labor onset, in line with our findings of no correlation between placenta-associated biomarkers and chorioamnionitis signs. In healthy pregnancies at term, the overall rate of histologic chorioamnionitis has been reported to be 34–42% [36,50], which is comparable to the 49% found in our healthy post-date pregnancies. Clinical chorioamnionitis is a rare event in term deliveries, reported in up to 4% [51], and comparable to the 3.4% found in our study. Chorioamnionitis is associated with failure to progress during delivery, possibly caused by ineffective uterine contractions due to inflammation [52], representing a common cause of cesarean section at term [53]. In line with previous studies, we also observed longer duration of labor in those with histopathological signs of acute chorioamnionitis [53].

4.2. Strengths and limitations

There are several strengths in our study. The investigators were blinded for maternal and fetal characteristics as well as pregnancy and delivery outcome, thereby limiting the chance of bias when evaluating the morphological findings in the placentas. We applied the Amsterdam Workshop Consensus Criteria [18] to classify lesions, thus making study results internationally comparable to other studies using the same criteria. In addition, we used criteria from Turowski and Vogel [11] for the evaluation of maturation disorders to better describe features of delayed maturation. Among the limitations is that every fifth placenta was sent to pathological examination, but this random selection has likely not biased the study cohort. Ethnic heterogeneity in our study population is limited, as the participating women were primarily white due to language inclusion criteria (Norwegian or English).

5. Conclusion

Post-date placentas from uncomplicated pregnancies without adverse delivery outcomes show signs of oxidative stress, represented by increased intervillous fibrin depositions, increased syncytial knotting, villous infarction and distal villous hypoplasia, all signs of maternal vascular malperfusion. These morphological changes were associated with lower maternal circulating PlGF, and higher sFlt-1 and sFlt-1/PlGF ratio, thus a more antiangiogenic maternal phenotype prior to delivery, similarly to what is seen in early-onset placental syndromes, i.e. preterm fetal growth restriction and preeclampsia. In addition, the majority of the post-date placentas showed delayed villous maturation, which may suggest that delayed maturation biologically facilitates prolongation of pregnancy to continue past term. The maternal antiangiogenic profile is more increased in post-date pregnancies with adverse placenta morphological findings (albeit no adverse clinical outcomes), indicative of maternal vascular malperfusion and thus increased cellular stress. We therefore suggest that these placenta-derived biomarkers may represent a new clinical tool to estimate the reserve capacity of the placenta and thereby assist in the clinical handling of post-date pregnancies to prevent adverse delivery outcomes.

Ethics approval

National research ethical and institutional bodies have approved the PREPPeD (PREdelivery Placental biomarkers – Pregnancy and Delivery outcome) study, which the present study is part of (REK South-East D ref 2016/652). The PREPPeD biobank is coordinated as a thematic biobank within the Oslo Pregnancy Biobank (OPB; REK Eastern Norway, ref 529–02162). The PREPPeD study is registered at ClinicalTrials.gov, identifier NCT0310008.
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References


