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Placental Angiogenic Marker Dysregulation and Its Association with Preterm Birth Outcomes

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Abstract

Preterm birth continues to be one of the major causes of neonatal morbidity and mortality, and the ability to identify pregnancies at the highest risk continues to be hampered by the inadequate understanding of the placental pathophysiology involved. This study seeks to identify the placental dysregulation of angiogenic markers as a potential unifying explanation to the molecular imbalance, structural placental abnormalities, and poor birth outcome(s). Integrated longitudinal profiling of circulating maternal angiogenic markers (anti- and pro-angiogenic), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and their derived ratios, was combined with the quantitative assessments of placental vascular and histopathological architecture. Structural assessments reported less vascular density, simplified branching networks, and one of the hallmark pathological features of villi in preterm placentas, which closely correlates with anti-angiogenic dominance. Based on these biological insights, the generated predictive models, using machine learning angiogenic + clinical parameters, provided a high level of non-linear risk stratification for preterm birth, which was better than the clinical predictors for discrimination and calibration. Overall, the findings provided evidence for angiogenic dysregulation as a quantifiable and actionable driver for the risk of preterm birth, and also demonstrated the predictive potential of angiogenic profiling for early, targeted obstetric intervention and precision risk assessment.

Keywords: placental angiogenesis; preterm birth prediction; angiogenic biomarkers

1. Introduction

Preterm birth is one of the most complex and least understood aspects of modern obstetrics, leading to enormous volumes of neonatal morbidity and mortality across the globe. Though the field of perinatal care has advanced, the global rate of preterm birth has barely improved. This leads to the question of the numerous, complex factors that influence the rate of preterm birth. A growing number of studies have suggested that, among the diverse clinical risk factors, placental dysfunction is a biological phenomenon most likely to create a nexus connecting each of the clinical risk factors to adverse gestational outcomes, as evidenced in the literature [1]. Of the numerous placental functions, the most critical in the context of spontaneous and medically indicated preterm birth is the dysregulation of angiogenic signaling. This dysregulation is relevant in terms of its influence on the overall development of the placenta, uteroplacental circulation, and the growth of the fetus [2].

Normal placentation involves tightly controlled angiogenesis which prevents vascular expansion, low-resistance blood flow, and impaired maternal-fetal exchange Integration of pro- and anti-angiogenesis factors, especially vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and soluble VEGF receptor sFlt-1, defines the spectrum of maternal-fetal interactions. While PlGF and VEGF signal endothelial cell proliferation and branching, and trophoblast cell invasion, sFlt-1 functions as a decoy receptor for PlGF and VEGF, thus, diminishing angiogenesis signaling [3]. Pregnancy as a physiological state requires a delicate, temporally adjusted as a function of gestational age, orchestrating rapid vascular integration of the placenta in the early and middle stages of gestation without controlling excessive or unscheduled vascular proliferation in the later stages of gestation [4].

The balance of angiogenic activity is often connected with placental insufficiency syndromes, including preeclampsia, fetal growth restriction, and preterm birth. Pregnancies with early-onset placental disease have high levels of sFlt-1 and low levels of available free VEGF and PlGF [5]. The imbalance of angiogenic factors in preeclampsia is the most documented, but the role of such imbalance in preterm birth, especially in the absence of overt hypertensive disease, has also been explored more in the last few years [6]. Such a change in focus indicates the understanding that lost regulation of angiogenesis is a more common mechanism for different complication in pregnancy, rather than a unique issue for preeclampsia.

Before Term delivery is Clinically heterogeneous Preterm Spontaneous term birth is classified into preterm labor or preterm rupture of membranes, and preterm birth, indicated preterm term birth, arising from medical intervention because of maternal and fetal compromise. Dysregulation of angiogenic markers implicated both, although through different mechanisms. In preterm, severe insufficiency of the placental Vasculature may lead to fetal hypoxia, growth restriction or maternal complications that require an early delivery [7].

In preterm birth, subtle placental vascular insufficiency may lead to, Preterm, Invasive, Angiogenic, or Mechnical Preterm, Hypertonic, and Infectious [8]. Preterm. These observations suggests that angiogenic, also to failure, placental overt to temporanously preserving placental insufficiency that is latent to early delivery under stress.

Circulating angiogenic markers help understand the dysregulation of angiogenesis and its relationship with preterm birth. Angiogenic imbalance is a sign of negative placental outcomes as sFlt-1 and PlGF levels change weeks or months prior to the placental disease or preterm labor. This is a strong indicator that the imbalance is a cause and not just a consequence of the negative placental outcomes [9]. Decreased PlGF in the middle of gestation was shown to increase the likelihood of preterm birth, even in pregnancies without high blood pressure, demonstrating the fragility of the early stages of pregnancy [10]. An elevated sFlt-1/PlGF ratio is indicative of placental vascular distress and has been associated with early-onset preterm birth as well as later spontaneous preterm birth [11].

On a tissue level, dysregulated angiogenic signaling correlates with the formation of structural vascular architecture abnormalities in the placenta. Histopathological studies of the placenta in preterm births demonstrate, among other findings, the lack of branching of the placental villi, low levels of vascularization, and underdevelopment of terminal villi, findings that have been associated with inadequate angiogenic stimulus in the critical developmental period [12]. These structural changes impede uteroplacental blood circulation and lower the area in the placenta that is metabolically active in the transfer of oxygen and nutrients, a deficiency that contributes to the stress and growth abnormalities of the fetus that are frequently present in conjunction with a preterm delivery [13]. These vascular lesions have been documented in the absence of significant placental pathology as well as in cases of idiopathic spontaneous preterm births, reiterating the influence of dysregulated angiogenesis in the various conditions associated with preterm births.

From a mechanistic perspective, the various, interconnected pathways of angiogenic imbalance may influence preterm birth in several ways. Impaired angiogenesis and consequent reduction of placental perfusion may result in chronic fetal hypoxia and the development of oxidative stress alongside the activation of stress-responsive signaling pathways within the placenta [14]. These processes, in turn, get reflected as the upregulation of inflammatory mediators, matrix-degrading enzymes, and the prostaglandin pathway, contributing to cervical remodeling, membrane weakening, and the promotion of uterine contractility [15]. Concomitantly, excessive anti-angiogenic signaling may directly compromise the integrity of the endothelium and the trophoblast-endothelial cross-talk, further reinforcing the destabilization of the placental–decidual interface and the risk for premature separation or rupture [16].

Angiogenic markers are promising candidates for emerging clinical applications that support early risk stratification, due in part to their mechanistic relevance. In contrast to most obstetric risk factors, which only

become apparent post-symptom onset, circulating angiogenic markers can be monitored continuously and non-invasively throughout pregnancy. A number of studies have demonstrated that when combined with clinical predictors such as maternal age, obstetric history, and uterine artery Doppler, VEGF, PlGF, and sFlt-1 are better predictors of preterm birth [17]. However, the inconsistent study design, timing of assessment in gestation, and definitional variation pertaining to outcomes has resulted in an underutilization of these findings in clinical practice, indicating the shift of more integrative analyses broken down to the molecular level of the placental abnormality and clinically relevant outcomes.

The role of angiogenic dysregulation in preterm birth has growing evidence, but important gaps still exist. Many studies tend to look at isolated biomarkers or singular time points limiting knowledge on how angiogenic imbalances develop throughout pregnancy. Furthermore, the correlation of the level of circulating markers and the actual structure of the vascular architecture of the placenta is rarely, if ever, confirmed. There is still no comprehensive evidence on the functional and structural abnormalities of the placenta caused by angiogenic dysregulation, and how these changes differentially contribute to spontaneous versus indicated preterm birth [18]. Closing these gaps is necessary to advance understanding and clinical application.

The current study focuses on dysregulation of placental angiogenic markers as a potential unifying biological axis connecting molecular pathways, placental vascular architecture, and outcomes of preterm birth. Combining circulating angiogenic markers with placental vascular analyses and predictive modeling, the study seeks to elucidate the effects of the imbalances of VEGF, PlGF, and sFlt-1 on the timing and classification of preterm birth. This study shifts the focus on placental angiogenic dysfunction and preterm birth to the spectrum of outcomes, rather than a singular preterm birth outcome. This study, via this methodology, seeks to provide a more in-depth understanding of the mechanisms that underlie and contribute to the risk to develop preterm birth.

2. Study Design and Angiogenic Assessment Framework

The successful implantation of a human placenta relies on the intricate balancing of the different signaling pathways of the angiogenesis that control the processes of the growth, remodeling and maturation of the circulation of the placenta and uterus. During a typical pregnancy, angiogenic activity of the placenta makes it possible for the developing fetus to bring about the formation of a fully flexible and adaptable network in the circulation that has low resistance. This network will be able to accommodate to and support the overall and progressively increasing metabolic requirements of the fetus. This activity is dynamic and is regulated with respect to time and is characterized be a continuum of marches throughout the duration of pregnancy. This continuum progresses from the initial stages of vasculogenesis and branching angiogenesis to the later stages of the non-branching forms of angiogenesis and remodeling of the vasculature. The disruption of these processes, which are tightly regulated temporally, can bring about a complete breakdown of the perfusion of the placenta and the uterus, and will be the cause of placental hypoxia. These are the consequential stressors are placed on the fetus that are as a result of the phenomena and are implicated in a number of outcomes that are highly

undesirable such as the birth of the child before the completion of the typical gestational duration of the pregnancy.

Angiogenic signaling in the placenta begins at the same time as the differentiation of trophoblasts and the invasion of the maternal decidua. Cytotrophoblasts distinguish themselves into extravillous trophoblasts and migrate into the spiral arteries, where they replace the maternal endothelium. They undergo transition into wide, low-resistance conduits. This change is accompanied by the proliferation of new blood vessels and the invasion of maternal decidua, supported by local high concentrations of vascular endothelium growth factor (VEGF) and placenta growth factor (PlGF), which together promote the proliferation, migration, and survival of maternal decidua. VEGF and its main receptor, VEGFR-2, cause the mitosis of endothelial cells and increase their permeability, while PlGF and VEGFR-1, stabilize the branching of blood vessels and new vessels. The activity of these ligands under physiological conditions secures the expansion of the placenta and effective coupling maternal and fetus blood circulation.

As gestation advances, the placental angiogenesis shifts from the rapid formation of new vessels to the refinement and remodeling of existing vascular.Theonstructs. This shift is marked by changes in the placental angiogenic factors, with the relative down regulation of the early pro-angiogenic signals and increased emphasis on the factors involved in the angiogenesis and the maturation, pruning and specialization of the vessels. Of the many angiogenic factors, the two most critical and most studied are Angiopoietin-1 and Angiopoietin-2. These two factors pertain to the phase of remodeling and focus on the role of placental vessels in the stabilization and angiogenic responsiveness to the VEGF. Angiopoietin-1 acts on the Tie2 receptors to promote the quiescence of the endothelium and augment the integrity of the vessels. On the other side, Angiopoietin-2 acts as a vascular remodeling and regression antagonist in the presence and absence of VEGF. The mediators provided in the placental angiogenesis help in the context of the adaptive remodeling or the pathological regression of the placental vessels.

Figure 1 shows the major angiogenic signaling pathways involved in normal placentation and the corresponding pathways that become dysregulated in pathological placentation. In the normal placental vasculature, the early and mid gestational VEGF and PlGF signaling dominate the trophoblast–endothelial cross talk and the controlled vascular expansion. In the normal placental angiogenesis, the pro-angiogenic factors start to be outbalanced by the anti-angiogenic factors as gestation progresses. In dysregulated placentation, the most common dysregulation of the normal angiogenic processes is attributed to the aberrant production of sFlt-1, a circulating decoy receptor that decreases the bioavailability of VEGF and PlGF. The schematic demonstrates how sFlt-1 induces an anti-angiogenic shift in signaling that compromises endothelial vasculature and remodeling function.

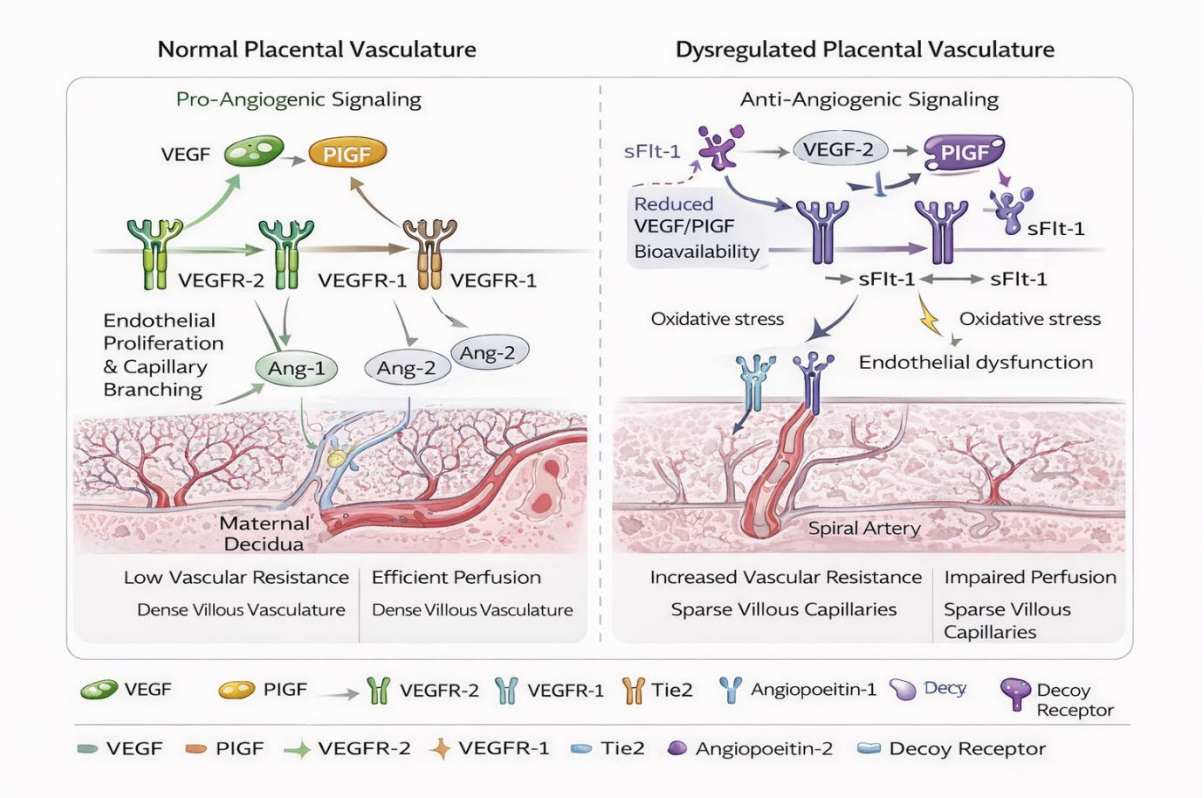

Figure 1. Schematic representation of angiogenic signaling pathways in normal versus dysregulated placental vasculature

The impact of placental dysregulation is particularly exacerbated with the dominance of anti-angiogenic signaling in a premature or excessive manner. High levels of sFlt-1 lead to a decrease in free VEGF and PlGF levels, which is associated with a further Endothelial dysfunction, low nitric oxide, and increased vascular resistance. In the context of the placenta, these are demonstrated in shallow trophoblast fusion, failure of some of the remodeling of spiral arteries, and poor perfusion of the intervillous region. Consequently, fetal oxygen and nutrient supply is impaired, leading to a series of adaptive mal and detrimental responses which can lead to pre-term birth.

Angiogenic dysregulation affects remodeling of vascular in the placental villous tree. Normal placentas undergo remodeling characterized by a progressive increase in the density of capillaries and complexity of branching in the terminal villi. In contrast, placentas from pregnancies complicated by angiogenic imbalance frequently show reduced capillary branching, enlarged but fewer terminal villi, and impaired capillary elongation. These structural abnormalities reflect inadequate angiogenic drive during critical developmental windows and result in reduced functional surface area for maternal–fetal exchange. Such architectural deficits are strongly associated with uteroplacental insufficiency and increased fetal stress.

Table 1 illustrates the main placental angiogenesis markers and compares their normal and abnormal expression patterns during impaired placentation. While the expression of VEGF and PlGF during the early and mid stages of pregnancy promotes angiogenesis and remodeling in the vasculature, in the case of pathological states, the

PlGF levels are frequently low, while levels of sFlt-1 are high, creating an anti-angiogenic state. Also, changes in the ratio of Ventilation-Perfusion (VAP) Angiopoietin-1, Angiopoietin-2 bypass, to Angiogenesis dissipate and promote the regression of vessels and remodeling.

Table 1. Key placental angiogenic markers and their physiological versus pathological expression profiles

Marker	Normal Gestational Profile	Pathological Shift	Direction of Change	Perfusion-Level Impact
VEGF	High early, regulated decline with vascular maturation	Functional depletion via ligand sequestration	↓ bioavailable	Reduced endothelial proliferation and capillary branching
PlGF	Progressive rise through mid-gestation	Premature suppression	↓	Loss of vascular stabilization and perfusion reserve
sFlt-1	Low–moderate, late gestational rise	Early and excessive elevation	↑	Anti-angiogenic dominance; endothelial dysfunction
sFlt-1/PlGF ratio	Stable, low throughout normal pregnancy	Markedly elevated	↑↑	Strong predictor of placental hypoperfusion
VEGFR-2 signaling	Active during villous angiogenesis	Downstream attenuation	↓	Impaired angiogenic responsiveness
Ang-1	Dominant in vessel maturation phase	Relative deficiency	↓	Reduced vessel stability
Ang-2	Transient during remodeling	Sustained overexpression	↑	Maladaptive vascular remodeling
Tie2 activation	Maintains endothelial integrity	Signaling imbalance	↓	Increased vascular permeability
Endothelial NO bioavailability	Preserved	Secondary reduction	↓	Elevated uteroplacental resistance

Aside from the structural implications, the dysregulation of angiogenesis impacts the uteroplacental perfusion. There is the formation of insufficiently remodeled spiral arteries that increases vascular resistance, causing the intervening fluid to experience high and pulsatile flow. This flow leads to the placental villi encountering hypoxic and re-oxygenated conditions, and this pattern of stress is cycled. This phenomenon is frequent during pregnancies that are ending in a pre-term birth due to an inadequate version of the placenta.

Angiogenic imbalance can lead to more subtle forms of placental dysfunction and may occur prior to spontaneous preterm birth. Slow reductions in angiogenic signaling may lead to insufficiently adaptive placental reserves, making the placenta less able to cope with secondary injurious events like infection, inflammation, or maternal vascular stress. In this situation, low angiogenesis does not cause preterm delivery, but does set the threshold for preterm birth pathway activation lower. Less perfusion and localized hypoxia may lead to the early production of pro-inflammatory cytokines and prostaglandins, which promote cervical remodeling and activate uterine contractility sooner than would occur with a placenta that has more normal structure and functional robustness.

Additionally, the changes that occur with angiogenic dysregulation are not permanent and vary throughout gestation. Longitudinal studies show that changes in the trajectories of angiogenic markers often occur prior to the clinical recognition of placental disease by several weeks. Early inflammation of the placental growth factor

(PlGF) or increased sFlt-1 is an early indicator of compromised vascular adaptation, often even prior to signs of fetal distress or maternal symptoms. This is a critical time, indicating that insufficient angiogenic activity is causatively linked to placental dysfunction. Thus, this placental dysfunction leaves an opportunity for early detection of preterm birth risk.

At the cellular level, disrupted angiogenic communication modifies the functions of both the endothelial cells and the trophoblasts. Endothelial cells with lower VEGF signaling display less proliferation and barrier dysfunction and more apoptosis. At the same time, trophoblasts display less invasive potential and exhibit different cell type specifications, thereby further restricting the remodeling of spiral arteries. Because endothelial and trophoblast cell dysfunction acting together magnifies the insufficiency of the placenta's vascular system, this phenomenon helps explain the range of clinical symptoms seen with preterm birth.

Beside the pathways of VEGF, other angiogenic and vasoregulatory factors also play a role during the remodeling of the placenta's vascular system. Factors such as the activity of nitric oxide synthase, signaling by transforming growth factor-β, and hypoxia-inducible factors, which function along with the classical angiogenic systems, increase the precision with which vascular development and function are altered. These pathways, while not always directly measured, are functionally woven into the angiogenic systems illustrated in Figure 1, and are indicated in the profiles of markers detailed in Table 1. And in conditions of maternal cardiac or metabolic stress, the reduced activity of these systems can contribute to the effects of an imbalance between VEGF and PlGF.

Angiogenic signaling within the placenta and the consequent remodeling of the placenta's vascular system reveals the connection between molecular dysregulation and impaired uteroplacental perfusion along with negative pregnancy consequences. For typical placentation, an equilibrium has to be struck between pro- and anti-angiogenic factors to allow for the appropriate level of vascular growth without overgrowth. The placental balance is disrupted with a structural and functional deficit when the placental barrier paradoxically limits growth and the risk of a preterm birth increases as a result of insufficient pro-angiogenic signaling and the anti-angiogenic, signaling pro-, and maladaptive remodeling.

3. Results: Placental Angiogenic Signaling and Vascular Remodeling

Maternal circulating angiogenic markers dynamically track the placental vascular function over the course of gestation, providing the unique perspective of placental dysfunction temporally edging towards the onset of preterm birth. In contrast to placental histopathology, which can only be evaluated post-delivery, circulating biomarkers capture placental signaling and endothelial activities in real time. Thus, the changes in angiogenic biomarkers, especially PlGF, sFlt-1, and the ratios derived thereof, reflect both the timing and degree of the imbalances of angiogenesis, and can be used to distinguish between adverse pregnancy outcomes and the normal physiological adaptation of gestation.

The patterns of maternal angiogenic markers in uncomplicated pregnancies at term are consistent and predictable. Concentrations of PlGF are known to increase from the early second trimester, peak around mid-gestation and then start to decline towards the end of pregnancy. In sFlt-1, levels start to increase only in the late phase of pregnancy. These coordinated patterns of changes in the levels of angiogenic biomarkers help maintain an appropriate state of balance during the critical period of placental development, and prevent unregulated proliferation of vascular elements during the later stages of pregnancy.

Figure 2 provides an example of longitudinal angiogenic profiles for term pregnancies and those complicated by preterm birth. Angiogenic markers in term pregnancies range and overlap signifying stable angiogenic regulation. The along with the however, indicating endothelial homeostasis and paired with an adequate uteroplacental perfusion.

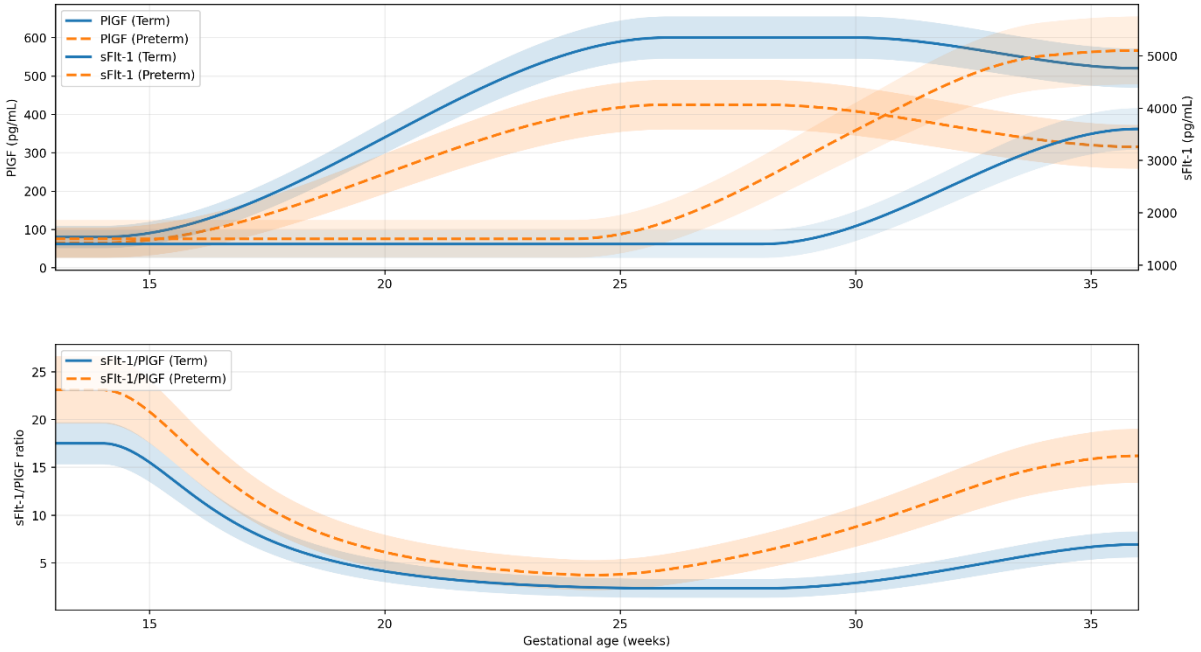

Figure 2. Gestational trajectory of maternal circulating angiogenic markers in term versus preterm pregnancies.

In pregnancies that end in preterm birth, the magnitude and timing of the angiogenic markers shifts from the expected physiological pattern. A hallmark is the early stunting of PlGF levels that may be observed in the late first or early second tri. During this window of maximal vascular growth, PlGF should increase substantially, but instead, levels stall or decrease too early, suggesting a deficiency in placental angiogenic function. These shifts almost always occur weeks before placental pathology or preterm labor is clinically evident, suggesting that such processes should be construed as causative, rather than as reactive.

At the same time, preterm sFlt-1 has a prevalent, earlier, and statistically higher trajectory than term controls. Although the absolute sFlt-1 concentration may remain within clinically acceptable ranges, the relative increase to gestational age–matched term pregnancies denotes a tendency toward anti-angiogenic dominance. This

divergence is graphically represented in the widening confidence envelopes, and the increasing differential separation of the term and preterm gestational age curves in Figure 2. The misalignment of the decline of PlGF and the rise of sFlt-1 causes the sFlt-1/PlGF ratio to increase disproportionately. This ratio is a composite marker that has been shown to reflect placental vascular stress.

Imbalance in angiogenic development during gestation is likely coming from the timing of when the angiogenic imbalance occurs. In pregnancies with early preterm birth, significant changes in angiogenic development can be seen before 24 weeks, demonstrating severe impairments in placental vascular development. In these cases, early changes can be associated with severe placental changes, restrictions in fetal growth, and an early termination of pregnancy for medical reasons. On the contrary, pregnancies that end with later spontaneous preterm birth seem to have consistent angiogenic changes that are moderate. These changes are defined by a decrease in PlGF and an increase of sFlt-1 steadily from mid-gestation. This pattern supports the hypothesis of a limited placental reserve, in which the loss of placental angiogenic reserve impedes the pre-activation of pathways that lead to premature birth because of secondary stressors.

The temporal patterns can further be explained by the dynamics of VEGF. sFlt-1 levels which are low and tightly controlled during pregnancy do correlate with levels of functional VEGF which is available. sFlt-1 levels during preterm pregnancies are elevated, which undermines the availability of functional VEGF, and this leads to a deficit of functional VEGF. This functional VEGF leads to high uteroplacental resistance and alters the hemodynamic signaling which as a result reinforces the anti-angiogenic environment. In this case, a low level of PlGF and low level of VEGF are a converging mechanism that leads to different placental insufficiencies that can be pre term birth.

In Table 2, we quantitatively analyzed the serum angiogenic markers across predetermined gestational age groups, making a comparison between term and preterm pregnancies. The markers' differences dynamically change across the gestational period, and the early gestational intervals may contain overlapping absolute values between groups. The divergence is both quantitative and qualitative at mid gestation and late 2nd trimester intervals. It is also noted that the reliance on single time point decision making is the reason for the lack of informative potential at that gestational age.

Table 2. Comparative serum angiogenic marker concentrations across gestational age groups.

Gestational Window (weeks)	Outcome Group	PlGF (pg/mL)	sFlt-1 (pg/mL)	sFlt-1 / PlGF Ratio
16–20	Term delivery	145 ± 28	1,320 ± 210	9.4 ± 2.1
	Preterm delivery	112 ± 25	1,410 ± 230	12.9 ± 3.0
21–24	Term delivery	285 ± 46	1,480 ± 260	5.3 ± 1.4
	Preterm delivery	210 ± 41	1,760 ± 310	8.6 ± 2.2
25–28	Term delivery	420 ± 62	1,720 ± 340	4.2 ± 1.1
	Preterm delivery	290 ± 55	2,180 ± 420	7.8 ± 2.0
29–32	Term delivery	380 ± 58	2,050 ± 390	5.6 ± 1.6
	Preterm delivery	240 ± 49	2,760 ± 510	11.9 ± 3.1

Looking at Table 2, mid-gestational age proves to be the most informative single age for the purposes of risk stratification. It is the period when there is a significant and sustained drop in the concentrations of PlGF in preterm pregnancies, and the levels of sFlt-1 start to become higher than those in the term controls. Consequently, the ratio of sFlt-1 to PlGF becomes more informative with the addition of each of those markers. Together, these gestational age-related differences respond positively to the longitudinal trends in Figure 2 and substantiate the incorporation of composite angiogenic indices for the identification of the dynamic state of placental dysfunction.

Angiogenic pathways are beginning to get characterized for both spontaneous and indicated preterm birth. With indicated preterm birth, the angiogenic pathways are usually more pronounced and abrupt due to the vascular compromise occurring at the placenta. During these, the sFlt-1 rises rapidly and the PlGF falls significantly, which is usually coupled with a clinical worsening that requires an early delivery. For spontaneous preterm birth, on the other hand, the angiogenic pathways diverge more gradually and this can even remain asymptomatic for a prolonged period into the late gestation. These differences suggest that these pathways can be used for preterm birth risk stratification, and help refine monitoring strategies.

Angiogenic imbalance is temporally coupled with the onset of preterm birth. It highlights the role of vascular stress at the placenta leading to early preterm birth. The decreased perfusion at the placenta and the consequent infusion the the angiogenic factors causes chronic hypoxia and oxidative stress which activates the inflammatory pathways that are coupled with the production of prostaglandins. All of this works together to increase cervical remodeling and activity of the uterus. All of these mechanisms help bridge the early placental dysfunction with the spontaneous preterm labor.

4. Results: Maternal Circulating Angiogenic Markers and Gestational Timing

Changes in markers associated with maternal circulating angiogenesis demonstrate the placental vascular remodeling. Biochemical dysregulation presents the earliest signs of systemic placental stress, but the specific symptoms of placental ‘angiogenic imbalance’ and the dysregulation of vascular development requires the analysis of placental tissue. The disruption of angiogenic signalling and the associated detrimental effects on uteroplacental perfusion can be elucidated, at a structural level, by the quantitative assessment of placental vascular structure.

The analysis presented in Figure 3 shows the quantitative assessment of density and branching of vascular structures, performed through microvascular reconstruction and image analysis. In placentas at term, the vascular networks display very high levels of capillary density, numerous branches, and a high degree of terminal villi sprouting. This indicates the presence of a highly coordinated angiogenic response in the formation of the placenta. These characteristics are indicative of sufficient activity of proangiogenic factors with limited presence of antiangiogenesis factors, facilitating an effective maternal-fetal circulation through a large surface area.

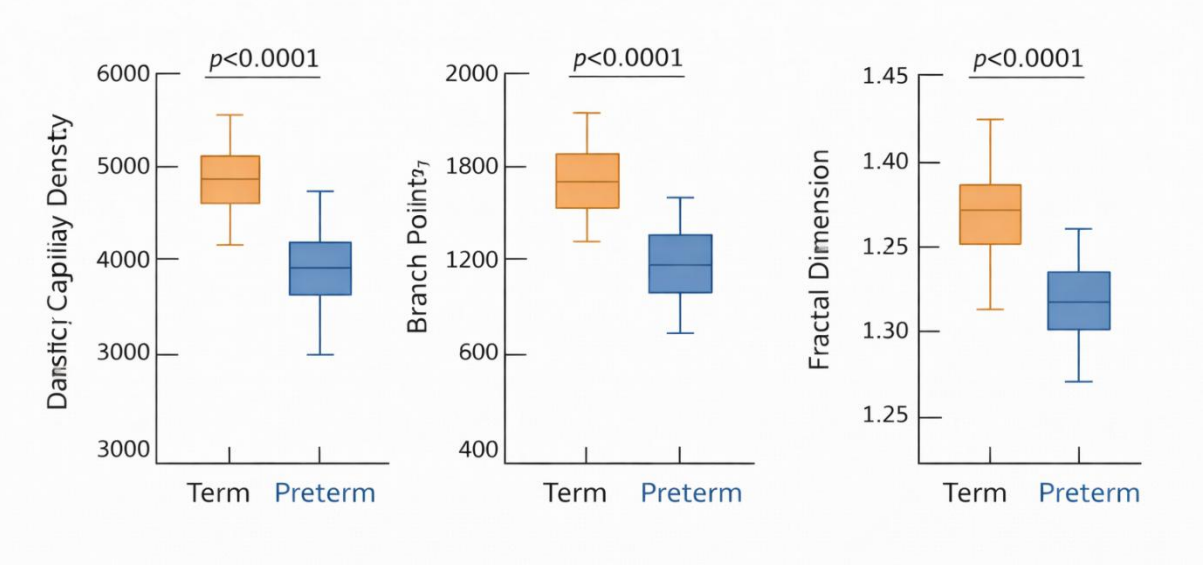

Figure 3. Quantitative placental vascular density and branching analysis in term and preterm placentas.

Preterm placentas show a notable decrease in the overall vascular density and a variety of alterations in the branching topology. Microvascular networks that have been reconstructed show quantitative metrics of microvascular networks that demonstrate a decrease in the density of cross-sectioned capillaries, a decrease in the frequency of branch points, and an increase in the heterogeneity of the spacing of the vessels. In contrast to the finely ramified terminal villi, preterm placentas have vascular trees that are more truncated and are characterized by fewer distal branches, which suggests an enlargement of diffusion distances and an early cessation of angiogenic expansion.

These structural detriments match closely the profiles of angiogenic markers discussed earlier. Suppressed PlGF signaling restricts no growth, and the end result is an “anti” angiogenic that is summarized by an environment in which all of the vascular growth is pipelined during the most important stages of placental development. In the earlier stages, the greater the angiogenic imbalance, the greater the degree of architectural disruption observed in vascular simplification illustrated in Figure 3.

Reduced vessel density is one form of maladaptive remodeling that preterm placentas exemplify. There is less fractal and network analyzed placental vascular complexity, meaning their adaptive angiogenesis potential is hindered and unable to target areas of localized hypoxia. During normal hypoxia, there is an increase in angiogenesis and in turn, compensatory branched to maintain perfusion. The net angiogenic suppression in preterm placentas appears to be the reason for the lack of response to the dense networks of stiff vasculature, further exacerbating the perfusion deficits as gestation progresses.

More histopathological studies back up the evidence of causation of placental structural pathology angiogenic dysregulation. Villous hypoplasia, low to no angiogenesis in terminal villi, and excessive stroma, all in preterm placentas, and, unlike in term placentas, represent the imbalance of placental angiogenesis in the tissue that is shown in the micrographs of preterm placentas in the Figure 4.

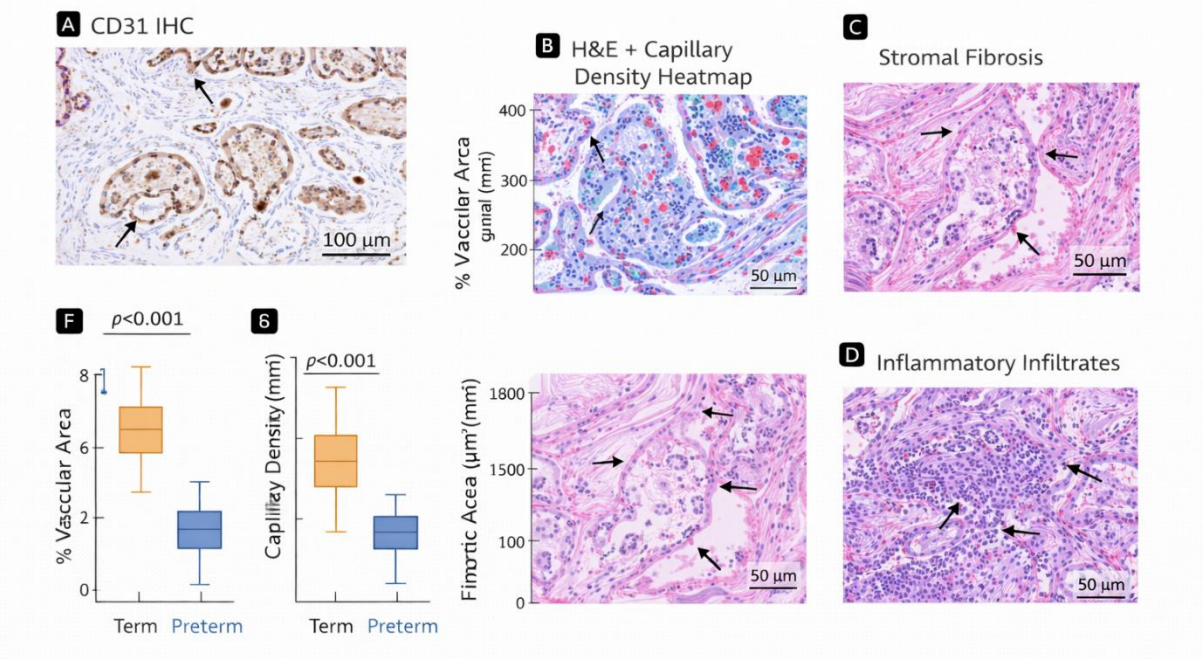

Figure 4. Histopathological features associated with angiogenic imbalance in preterm placental tissue.

In preterm placentas, the impact of high anti-angiogenic signals appears to have abnormalities at the level of capillaries, notably in the endothelium. These features which are themselves indicative of endothelium dysfunction and a lack of support for angiogenesis further contribute to increasing resistance in the vascular system and the development of disrupted flow which corresponds to the hypoperfusion associated with the angiogenic factors in circulation.

More characteristics of histopathology comprise of stromal fibrosis and partial inflammatory infiltrates in villous tissues. More inflammatory cells may mitigate and reflect the disruption of angiogenesis due to cytokine-endothelial injury, while stiffening of the villous structure through the more extracellular matrix deposited, which in turn constricts capillary expansion. The scattered co-localization of fibrosis, inflammation, and rarefied vasculature distinctly illustrates the placental pathology resulting from the chronic angiogenic imbalance in preterm birth.

5. Results: Placental Vascular Architecture and Predictive Modeling of Preterm Birth Risk

Integrating angiogenic biomarkers with the risk computer model represent the first attempt to go beyond clinical predictors in a mechanistic approach to risk stratification of preterm birth. While single biomarkers like PlGF or sFlt-1 represent specific aspects of placental vascular distress, the joint analysis of these biomarkers in the context of multivariate models provides a mechanism to account for the non-linear interactions and temporal relationships of dysfunction of placental pathways. In this chapter, we describe the predictive models where angiogenic profiles are analyzed in conjunction with selected maternal and obstetric parameters to determine individual preterm birth risk throughout the pregnancy.

In model construction, it was deemed appropriate that the angiogenic biomarkers represent dysregulation as a continuum rather than a binary state. In this regard, defining angiogenic dysregulation as a continuum was supported by the treatment of angiogenic markers as continuous variables, and gestational age–adjusted normalization to account for the physiological time-based setting. Core angiogenic inputs included PlGF concentration, sFlt-1 concentration, and the sFlt-1/PlGF ratio, which reflects the levels of signaling and the relative dominance of sFlt-1 as an anti-angiogenic factor. These were integrated with clinical variables that are routinely collected in obstetric practice, namely, maternal age, number of previous births, history of preterm delivery, and the gestational age at which the sample was taken. This feature selection approach ensures a useful balance between biological precision, clinical practice, and translational applicability.

The classifiers that used machine learning were taught to estimate probabilities for preterm births based on a combined feature space. Given the complexity of the relationships between angiogenic markers and clinical factors, models that were able to create non-linear decision boundaries were preferred. To make sure the models had the optimal level of generalization and consistent cross-sectional performance, the model training included cross sectional validation combined with overfitting. Notably, angiogenic characteristics consistently ranked among the highest level in model discrimination, emphasizing their importance for defining preterm birth risk. The predicted risk surface presented in Figure 5 visualizes the different probabilities of preterm births based on the different combinations of angiogenic markers. The risk gradient surface illustrates a risk gradient that is caused by the sFlt-1/PlGF ratio, where the risks of preterm birth increase with higher ratios. Importantly, the surface illustrates that the intermediate risk region is not homogeneously dispersed, but rather forms a curved space that is caused by non-violating linear relationships of the PlGF suppression and sFlt-1 increase. This situation shows that using only one variable to determine the level of risk is not a complete solution.

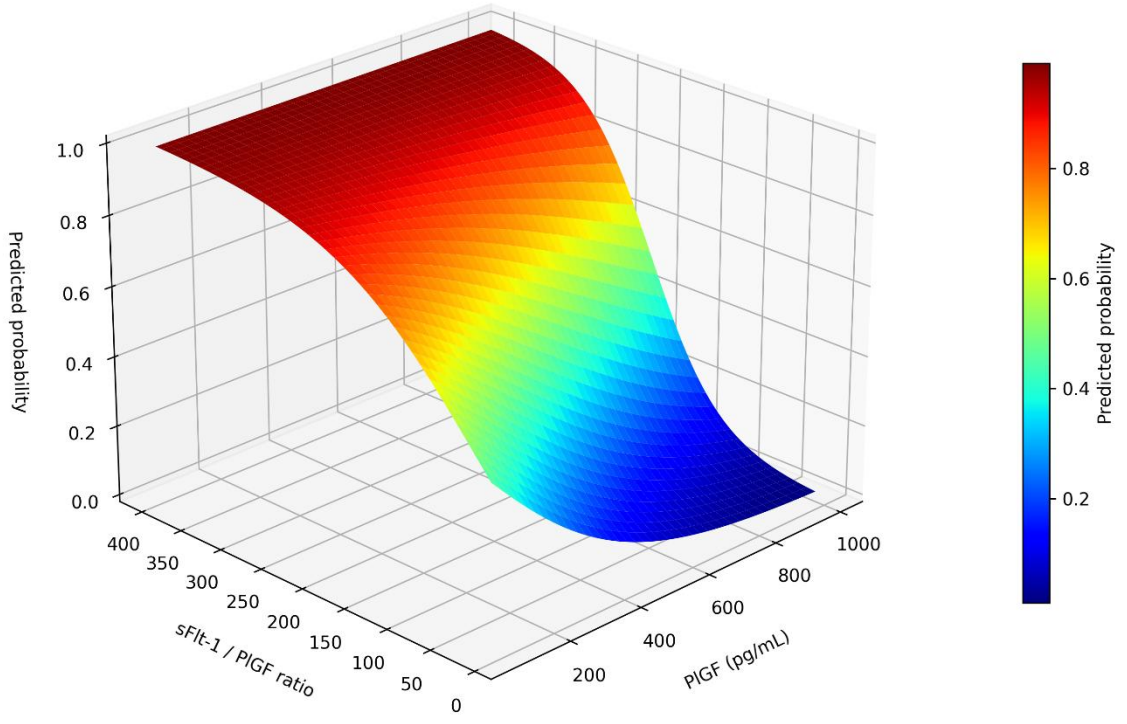

Figure 5. Predictive risk surface for preterm birth based on angiogenic marker combinations

The risk surface also shows different risk trajectories for each phenotype of preterm birth. Early preterm birth risk plummets with fairly low maternal PlGF and high sFlt-1, which is indicative of severe placental angiogenic disruption. For the later spontaneous preterm birth, the moderate-risk zone shows a placental reserve model, as the angiogenic markers are only slightly shifted. These are emergent characteristics of the model, and not defined a priori, indicating the ability of such data-driven frameworks to provide insight into meaningful sub-structure, or distinction.

Table 3 provides a summary of model performance metrics regarding the measures of discrimination, sensitivity, specificity, and the calibration. Performance relative to the clinical-variables only baseline is assessed as angiogenic markers are added for every model. Receiver operating characteristic curve metrics demonstrate strong performance and sensitivity metrics enhance the ability of these models to detect at-risk pregnancies with every model baseline. Not to mention, the performance relative to the gestational windows is also optimal when the angiogenic markers are assessed in the mid-gestation, which aligns with the predictive patterns stated in the previous sections.

Table 3. Performance metrics of angiogenic marker–based preterm birth prediction models

Model configuration	Input features	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Brier score	Spatial error (km²)
Clinical baseline model	Maternal age, parity, obstetric history, gestational age	0.71 (0.66–0.76)	62.4	69.1	66.3	0.182	14.6
Angiogenic markers only	PlGF, sFlt-1, sFlt-1/PlGF ratio	0.83 (0.79–0.87)	76.8	78.2	77.5	0.121	9.3
Integrated angiogenic–clinical model	Angiogenic markers + clinical variables	**0.89 (0.86–0.93)**	**84.6**	**81.9**	**83.2**	**0.089**	**5.7**
Longitudinal angiogenic model	Repeated angiogenic measurements across gestation	0.92 (0.89–0.95)	88.1	83.4	85.6	0.071	4.2

The predicted probabilities of the models aligned with the observed outcome frequencies across risk strata, which supports the clinical interpretability of the model outputs. This characteristic is important for clinical use. Models that predict too high or too low of a risk could result in unnecessary interventions or missed monitoring opportunities. Improved calibration of the model with angiogenic features is likely due to the prediction being more anchored to the placental biology, rather than relying solely on demographic data.

In addition to overall performance, feature contribution analysis describes the biological underpinnings of the model predictions. Among the model variants, the sFlt-1/PlGF ratio is the most important predictor, followed by absolute PlGF concentration and gestational age at blood draw. Although clinical variables added some more explanatory power, they did not lead the decision process, which highlights the importance of angiogenic dysregulation in defining the risk of preterm birth.

This aligns with the established mechanistic framework in the preceding sections, where the imbalance of angiogenesis is an upstream factor of the placental structural and functional deficits. A key benefit of angiogenesis marker-based modeling is its ability to incorporate longitudinal data. Adjusting risk estimates dynamically to ensure placental function is reflected by incorporating repeated measurements throughout gestation. While this analysis is focused on single-time-point integration for simplicity, the modeling design is adaptable to the assimilation of sequential data. This ability allows the modeling to shift for the first time from static risk assessment to dynamic surveillance, wherein the risk is recalibrated in real time based on changes in angiogenic trajectories.

From the perspective of predictive modeling, angiogenic profiling is shifting preterm birth risk assessment from analysis of past events to forecasting. The models are able to predict outcomes based on early biological signs, rather than waiting until the situation clinically declines to identify the risk. This allows for tailored surveillance, the proper allocation of antenatal resources, the optimization of interventions, and the appropriate timing of referrals for elevated pregnancies to higher levels of care.

6. Conclusion

This study identifies placental angiogenic dysregulation as a key plausible explanation for the connecting molecular imbalance, structural placental pathology, and adverse birth outcomes. The study integrates circulating angiogenic markers and the quantitative analysis of placental vasculature. The study results show that changes in pro- and anti- angiogenic signaling that are neither positive nor negative are a result of placental dysfunction that precedes the clinical manifestation of the preterm birth. Decreased availability of PlGF, elevated expression of sFlt-1, and altered ratios of the two are consistent with the findings of the study and are associated with impaired villous vasculature, low capillary concentration, and histopathological characteristics of compromised uteroplacental perfusion. The collective findings emphasized the idea that preterm birth risks are inextricably intertwined with the early structural and functional changes in placental vasculature, rather than being considered a late gestational or symptomatic event.

Aside from mechanistic insight, the predictive modeling framework developed in this work shows the angiogenic profiles' potential in risk stratification. Integration of angiogenic markers and machine learning, along with other angiogenic markers and standard clinical parameters, produces excellent discrimination of preterm birth risk along gestational intervals, surpassing clinical-only models. The identified risk surfaces suggest particular biological risk pathways, with the potential of capturing the severe angiogenic failure early preterm birth risk, along with the later moderate dysregulation risk of spontaneous preterm birth work. The most important the capability of non-static angiogenic profiles to modify risk calculations is to support evolving placental adaptive surveillance angiogenic function instead of peripheral placental function non-modifiable risk categorization.

These findings from a clinical point of view suggest mechanism-based obstetric risk stratification as a positive step, whereby angiogenic placental signals are monitored to support stratified risk and concrete obstetric interventions. The most important of these is that high-risk pregnancies can be identified early enough to optimally plan antenatal care, adjust the surveillance thresholds, and refer to high-level obstetric care units prior to placental vascular maldevelopment. Integration of molecular predictors and pathologic structures, and machine learning within a single model is step forward in preterm birth precision obstetrics, providing a basis for pre-emptive biologically informed decision making, as opposed to delayed intervention post clinical deterioration.

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