Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 695–697

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Case Report

Intrauterine growth restriction, soluble fms-like tyrosine kinase-1 to placental growth factor ratio increase and preeclampsia

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ARTICLE INFO

Article history:
Received 28 November 2018
Accepted 7 May 2019
Available online 11 May 2019

Keywords:
Fetal growth restriction
Intrauterine growth restriction
Preeclampsia
Soluble fms-like
tyrosine kinase-1
Placental growth factor

ABSTRACT

Background: Intrauterine growth restriction (IUGR) and preeclampsia (PE) share common features such as ischemic placental disease but also differ in their clinical expression regarding maternal diseases. The reason why IUGRremains isolated in some cases yet is followed by clinical manifestations of PE in other cases remains unexplained.
Case report: A 40-year old woman, gravida two, para one, experienced early-onset IUGR with a significant increase in the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) but, surprisingly, without any maternal clinical manifestations of PE.
Conclusion: IUGR and a significant increase in sFlt-1/PlGF ratio without PE raise the issue of a missing factor enabling IUGR, a significant increase in sFlt-1/PlGF ratio, and PE to be linked.
Teaching points: (1) Early-onset IUGR and a significant increase in sFlt-1/PlGF ratio do not necessarily mean the onset of PE. (2) Combining early-onset IUGR and a significant increase in sFlt-1/PlGF ratio without PE raises the question of an additional factor responsible for the onset of PE.

Introduction

Intrauterine growth restriction (IUGR) and preeclampsia (PE) share common features such as ischemic placental disease but also differ in their clinical expression regarding maternal disease. The reason why IUGR remains isolated in some cases yet is followed by clinical manifestations of PE in other cases remains unexplained [1]. Several hypotheses have been proposed to explain these different clinical pictures. Some authors claim that these two subsets of IUGR (with and without preeclampsia) could be attributed to a preexisting endothelial dysfunction fostered by a pro-inflammatory state with insulin resistance syndrome and oxidative stress that renders the endothelium more susceptible to imbalance of angiogenic factors [1,2]. We report herein a case of an early-onset IUGR with a significant increase in the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) but, surprisingly, without any maternal clinical manifestations of PE. We then discuss the various explanations for this inconsistency.

Case

A 40-year old woman, gravida two, para one, experienced, during her pregnancy, an early-onset IUGR before 34 weeks of gestation (WG) without clinical manifestations of PE. She had no past medical history. Four years ago, her first child was delivered by caesarean section at 37 W G due to an abnormal fetal heart rate. The patient delivered a small yet healthy baby girl who weighed 2530 g. During her current pregnancy, IUGR with hypotrophy below the 3rd percentile was revealed at 20.4 W G by routine ultrasound scan for fetal assessment. Uterine artery Doppler flow velocimetry performed at the same time revealed evidence of the vascular origin of IUGR with increased uteroplacental vascular resistance. The uterine diastolic index, expressed as the ratio of diastolic flow to peak systolic flow, and performed at 20.4 W G using Doppler ultrasound, was abnormal on both sides, with diastolic index values at 15% and 31% on the right and left uterine artery, respectively [3]. A search for notching was also performed and revealed the presence of a uterine notch on both sides. Subsequent Doppler ultrasound performed at 26.2 and 33.2 W G confirmed IUGR below the 3rd percentile with an abnormal diastolic index on the right uterine artery at 10 and 20%,

Abbreviations: IUGR, intrauterine growth restriction; PE, preeclampsia; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; WG, weeks of gestation; HELLP, hemolysis, elevated liver enzymes, and low platelet count; sEng, soluble endoglin.

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http://dx.doi.org/10.1016/j.jogoh.2019.05.007
2468-7847/

Table 1
Change in fetal biometry and uterine arteries Doppler according to gestational age in weeks of gestation.

Gestational age	20.4 WG	26.2 WG	33.2 WG
Fetal biometry	IUGR	IUGR	IUGR
Head circumference	6th percentile	30th percentile	10th percentile
Abdominal diameter	< 3rd percentile	< 3rd percentile	< 3rd percentile
Femur length	< 10th percentile	< 3rd percentile	< 3rd percentile
Uterine artery Doppler	Pathologic	Pathologic	Pathologic
Right uterine artery notch	Yes	Yes	Yes
Left uterine artery notch	Yes	No	No
Right uterine diastolic index	15% (pathologic)	10% (pathologic)	20% (pathologic)
Left uterine diastolic index	31% (pathologic)	43% (normal)	40% (normal)

respectively, and a normal diastolic index on the left uterine artery at 43 and 40%, respectively. A notch was also noted in the right uterine artery but not in the left one (Table 1). No biological disturbances in favor of PE were observed. Uric acid level was within the normal range for pregnancy, at 5.4 mg/dL (N < 5.8 mg/dL). Transaminases levels (ALT and AST) were at 14 and 11 international units/L (N < 40 international units/L), respectively. Serum creatinine level was at 0.53 mg/dL (0.6–1.1 mg/dL), which corresponded to an estimated creatinine clearance at 119 mL/min/1.73 m^2 using the CKD-EPI formula and 129 mL/min/1.73 m^2 using the MDRD formula. Neither proteinuria nor hemolysis were detected. On clinical examination, the patient's blood pressure level was normal, with a value at 128/85 mmHg (heart rate: 79 bpm). No edema was observed. Paradoxically, the serial sFlt-1/PlGF ratios calculated by BRAHMS KRYPTOR immunoassay were consistently and significantly high at 22.2 WG, 25.5 WG, 29.4 WG, 33.4 WG, and 34.4 WG, with values at 177.1, 90.3, 167.6, 222.8, and 236.9 respectively (Table 2) [4]. A healthy baby boy weighing 1226 g was ultimately delivered by caesarean section at 34.4 WG because of persistent IUGR without weight gain, decreased fetal activity, and heart rhythm disturbance. The baby's Apgar score was 10 and no distress respiratory syndrome was noted. No clinical manifestations of hypertension and proteinuria were observed throughout the pregnancy and after delivery. sFlt-1/PlGF ratio values dropped to 61.1, 57.9, 31.5, and 20.2 at 2, 3, 7, and 14 postpartum days, respectively (Table 2).

Discussion

This clinical case shows that, despite the absence of clinical features of PE, sFlt-1/PlGF ratio values were consistently above the diagnostic values defined for PE [4]. Indeed, sFlt-1/PlGF ratio threshold values for PE diagnosis are above 85 when pregnancy is within 20 WG and 34 WG, and above 110 when pregnancy continues until or after 34 WG with a specificity of 99.5 and 95.5% respectively [5]. Several non-exclusive hypotheses may be advanced as possible explanations for the lack of clinical manifestations of PE despite the significant increase in sFlt-1/PlGF ratio. One hypothesis is to presuppose that, in IUGR, various susceptibilities of maternal vascular endothelium to the imbalance of angiogenic factors can be observed and yield a set of different sFlt-1/PlGF ratio cutoff values that lead to clinical manifestations of PE. The varying susceptibilities of vascular endothelium to angiogenic imbalance may be attributed to other placenta-derived factors targeting vascular endothelium and inducing endothelial dysfunction. Previous studies have already highlighted the lack of perfect specificity and sensibility of sFlt-1 towards clinical manifestations of PE. In their first publication in 2003, on angiogenic factors, Maynard et al. stated in their title that excess sFlt-1 may contribute to endothelial dysfunction, hypertension, and proteinuria in PE but also suggested in their discussion that there might be other placenta-derived factors that could contribute to endothelial dysfunction [6]. The lack of adverse events such as IUGR or hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome in pregnant rats overexpressing sFlt-1 prompted the same research team to look for another angiogenic placenta-derived factor involved in these adverse events, which was identified as soluble endoglin (sEng) in a subsequent paper published in 2006 [7]. In a similar way, the lack of significant increase of circulating level of sFlt-1 observed in their study in a subset pregnant women with mild PE, points out the lack of perfect sensitivity of sFlt-1 towards manifest PE and leads the authors to suggest that other placenta-derived factors could be involved in the clinical manifestations of PE [6]. The lack of sFlt-1 specificity towards manifest PE had been also underlined by Stepan et al., in 2004, where a marked increase in the plasma sFlt-1 concentration of pregnant women with IUGR without surprisingly any clinical manifestations of PE was observed [8]. Among the factors that may contribute to endothelial dysfunction, Ness et al. suggest the possibility of a preexisting pro-inflammatory state with insulin resistance and oxidative stress to explain the onset of clinical manifestations of PE in some IUGR cases [2]. This assumption, however, faces a number of objections. Indeed, it is difficult to explain preexisting endothelial dysfunction in early-onset PE (< 34 WG) since it is usually observed during late-onset PE (≥ 34 WG), a subset of PE wherein, besides, IUGR is not typically observed. PE is traditionally divided into two subsets: early- and late-onset PE. From a clinical point of view, early-onset PE typically occurs in young, nulliparous, primigravida pregnant woman like a "bolt from the blue". Usually, neither metabolic syndrome nor preexisting vascular risk factors are found. This type of PE—which, therefore is also referred to as "placental PE"—seems to be rather immunologic than metabolic in origin. Early-onset PE is usually associated with IUGR. Conversely, late-onset or "maternal" PE, most commonly occurs among older, multiparous pregnant women with preexisting metabolic risk factors such as hypertension, overweight, obesity, and insulin resistance syndrome. This type of PE is usually not associated with IUGR. In both early- and late-onset PE, histological placental findings strengthen this classification since more histological abnormalities secondary to

Table 2
Change in sFlt-1/PlGF ratio values according to gestational age in weeks of gestation (WG) before caesarean section and in the postpartum period.

Gestational age	22.2 WG	25.5 WG	29.4 WG	33.4 WG	34.4 WG	Day 2	Day 3	Day 7	Day 14
sFlt-1 (pg/mL)	7334.0	5183.0	8143.0	11920.0	11560.0	1244.0	903.5	436.3	256.0
PlGF (pg/mL)	41.4	57.4	48.6	53.5	48.8	20.4	15.6	13.9	12.7
sFlt-1/PlGF ratio	177.1	90.3	167.6	222.8	236.9	61.1	57.9	31.5	20.2

defective extravillous trophoblast invasion are described in early- rather than in late-onset PE. Indeed, there usually are no histological abnormalities in the latter [9]. Among the previous studies carried out, several have already demonstrated that PE and IUGR provide similar "angiogenic" profiles characterized by a significant increase in sFlt-1/PlGF ratio compared to normal pregnancy even if, in most cases, the increase in sFlt-1/PlGF ratio during IUGR alone is of less significance than during PE [10,11]. Stepan et al. have compared circulating levels of sFlt-1 and sEng in normal pregnancy, normotensive pregnancy with IUGR and manifest PE [12]. They observed a significant increase of sFlt-1 and sEng in normotensive pregnancy with IUGR compared to normal pregnancy albeit less substantial than in manifest PE. These datas lead the authors to propose two interpretations, firstly sEng is mainly a phenomenon of PE and is to a less extend involved in IUGR, secondly IUGR and PE share the same physiopathological pathway but with a less pronounced increase of sEng and sFlt-1 in IUGR that did not reach the threshold for clinical manifestation of PE. However in our case report sFlt-1 /PlGF ratios were consistently, to a large extent, above the threshold for clinical manifestations of PE. Because of discordant clinical presentations between PE and IUGR despite similar angiogenic profiles, Alahakoon et al. had already suggested that other factors are required for the development of PE instead of IUGR alone [13]. Huppertz proposed another hypothesis that challenged the classic belief that PE and IUGR share exactly the same "placental ischemic disease" [1]. In "pure" early-onset vascular IUGR, only a failure of extravillous trophoblast invasion is observed, leading to abnormal uterine artery Doppler ultrasound, placental ischemia, and increased sFlt-1/PlGF ratio. However, in IUGR associated with PE or in PE alone, a failure of villous trophoblast differentiation is also observed. This phenomenon is responsible for releasing necrotic trophoblast fragments known as syncytiotrophoblast membrane fragments (STBM), which in turn induces a proinflammatory state with endothelial dysfunction and clinical manifestations of PE. The release of STBM is not observed during IUGR alone. A final additional explanation for the lack of clinical manifestations of PE could be a time lag between the occurrence of biological angiogenic imbalance and the outcome of clinical manifestations of PE. This hypothesis, however, is not confirmed in this clinical observation.

To conclude, the combination of early-onset IUGR with a significant increase in the sFlt-1/PlGF ratio does not necessarily mean the onset of PE. This specific situation must therefore be interpreted with caution and probably not in the same way as in conditions classically used for clinical suspicion of PE, such as pre existing chronic renal disease where hypertension and proteinuria are commonly observed and difficult to differentiate from super imposed PE. The absence of clinical manifestations despite a significant increase in sFlt-1/PlGF ratio leads us to assume the presence of one or several other placenta-derived factors that may contribute to explain endothelial dysfunction and the clinical manifestations of PE. Imbalance of circulating placental angiogenic factors illustrated by an increase in sFlt-1/PlGF ratio does not appear thus to be a sufficient, condition for the onset of maternal clinical manifestations of PE. One can even assume that the increase in sFlt-1/PlGF ratio may merely be a witness of ischemic placental syndrome and not the main player behind the occurrence of endothelial dysfunction and the clinical manifestations of PE. However, no other placenta-derived factors that may account for this discrepancy have been clearly identified to date. As noted earlier, some studies suggest that it could be explained by a concomitant increase of sEng or a release of STMB but a third placental derived factor cannot be excluded. Taken together, these clinical data indicate that IUGR alone, on the one hand, and PE (with or without IUGR), on the other, may not be the same placental diseases as they do not share exactly the same underlying physiopathological mechanism. Identifying this missing factor could make it possible to solve the equation connecting IUGR, increase in sFlt-1/PlGF ratio, and PE. It could also probably contribute to a better understanding of what differentiates early onset IUGR with PE from early-onset IUGR alone and close the gap that still remains between endothelial dysfunction and placental ischemic disease during PE.

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