Uteroplacental vascular syndromes: Theories, hypotheses and controversies

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Abstract

The maldevelopment of the spiral arteries in the placental bed reduces uteroplacental blood flow and results in diseases later in the pregnancy. These diseases are here called the uteroplacental vascular syndromes. These syndromes have serious consequence for both the infant and the mother. These pregnancies with a maldeveloped uteroplacental circulation can be detected in the first twenty weeks of pregnancy with uteroplacental Doppler studies. This predictive ability can be improved with addition of maternal biophysical and historical data and biochemical testing of the maternal blood. Prophylactic therapy with aspirin and other antioxidants improves outcomes in some if not all of these syndromes. The potential for these syndromes is probably 15% to 20% of nulliparous pregnancies. Further research needs to be done to clarify the above facts and thus better detect these pregnancies and improve interventions and outcomes. The research into the early detection and improving the outcomes of these pregnancies, with otherwise normal mothers and infants, takes a much lower financial profile than the early detection of abnormal foetuses.

Introduction

The maldevelopment of the spiral arteries in the placental bed occurs in up to 15-20% of nulliparous pregnancies with similar or higher rates in 'high-risk' multiparous pregnancies. The known and probable dynamics (pathophysiology) of how this maldevelopment goes to present as different syndromes, later in the pregnancy, is described. Drug prophylaxis can prevent or delay the clinical onset of these syndromes.

The syndromes are:

Pre-eclampsia (PE) / Eclampsia ('Toxaemia of pregnancy') – in most cases and in many case of Gestation Induced Hypertension (GIH); Preterm delivery (PTD) – in many cases and sometimes in Preterm Rupture of Membranes (PROM); Placental abruption – in many cases, also as antepartum haemorrhage (APH) in some cases; Fetal distress (FD) and Stillbirth (SB) – in many cases. Intrauterine growth restriction (IUGR) depending on the definition – this being the most controversial. The term "*Uteroplacental vascular syndromes*" (UPVS's) is a one which has been previously been called the 'Great Obstetrical Syndromes' [1], maternal placental syndromes [2], placental syndromes [3] and ischemic placental syndrome [4]. Uteroplacental vascular syndromes better describes the true nature of the pathophysiology of the disease process. We first described most of these syndromes having a common aetiology in an abnormal uteroplacental circulation (UPC) over 25 years ago [5].

The disease of 'toxaemia' of pregnancy (pre-eclampsia and eclampsia) and the other uteroplacental vascular syndromes are still major killers of, otherwise normal, mothers and babies in undeveloped countries of the world [6] but less so anymore in developed countries. Of pregnancies where the spiral arteries fail to undergo normal physiological change, only a quarter [7,8] go on to develop PE. PE occurs in 4.9% of nulliparous pregnancies [9]. Recently, early (first trimester) maldevelopment of the UPC in combination of chemical and biophysical maternal features has been found to have some clinical utility [10].

Incidences

Proteinuric hypertension (PE), in developed countries, has a rate of 5% in nulliparous pregnancies [9] and higher if case of non-proteinuric hypertension with either very high blood pressure or biomarkers such as hyperuricaemia. The rate is higher in 'high-risk' multiparous pregnancies [11]. In an unselected population the rate is 2% [7,8]. South African data just published is dramatically worse [4].

SPTD has a rate of 7% at <37 weeks and 2.5% at <33 weeks in nulliparous pregnancy, with additional cases of PROM [12]. Placental abruption has a rate 0.6% in nulliparous pregnancy [8] with additional cases of concealed abruption and APH with clinically undiagnosable abruption. FD rate was 3.3% in an unselected population [7] and a SB rate 1% of nulliparous pregnancies [9].

IUGR depending on the definition: on weight alone small for gestational age (SGA) below the 10th or 5th centile; asymmetric IUGR Ponderal Index below the 10th or 5th centile. We [13] and others [14] have FD rate is much higher for symmetrical IUGR than for SGA.

Compounding diseases

Diabetes Type 1: Sibai *et al.* [15] found that 20% of patients with insulin-dependent, pregestational diabetes develop PE.

Gestational Diabetes: Bryson *et al.* [16] that the Odds Ratio of pregnancies complicated with GD developing pregnancy related hypertension was 1.5 compared with the normal's.

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Obesity: found in nulliparous pregnancies with obesity, the rate of PE was 10.4% compared with 4.9% for all nulliparae [9].

Some degree of maldevelopment of the spiral arteries in the placental bed probably occurs in up to 15-20% of nulliparous pregnancies with similar or higher rates in 'high-risk' multiparous pregnancies [11].

The placental bed: physiology and pathophysiology

It is 60 years since Geoffrey Dixon and Tom Robertson (later; Ivo Brosens) started publishing their seminal works on the histology of the placental bed in normal and abnormal pregnancies with UPVS's [17]. In normal pregnancy in the placental bed "the spiral arteries after being breeched by the non-villous trophoblast, undergo extensive adaptations and structural alterations in order to provide the intervillous space of the growing placenta with an adequate amount of maternal blood [18]. This process they termed *'physiological change'*. Then "from 15 or 16 weeks' gestation, there seems to be a wave of intra-arterial trophoblast migration beyond the deciduo-myometrial junction into the true myometrial segments of the spiral arteries [19].

We were the first described and quantify the development of the normal low resistance circulation with Doppler changes in the UPC in mid-trimester normal nulliparous pregnancy [20]. All the indices of flow in the uterine artery flow velocity waveforms (UAFVW's) showed a continuous fall in resistance from 14 to 24 weeks.

The intimate interrelationship between the spiral arteries and the 'bush-like' placental cotyledons was beautifully described, photographed and illustrated by Wigglesworth almost 50 years ago (Figure 1) [21]. In the abnormal pregnancies with uteroplacental vascular syndromes, this invasion of the trophoblast into the myometrial segment of the spiral arteries fails to occur, the vesicles fail to properly dilate and the normal fall in blood flow resistance to the placenta fails to occur. In the third trimester, in some pregnancies these maldeveloped spiral arteries may further undergo disease changes similar to atherosclerosis. This of atherotic disease process was termed *'acute atherosis'* [22], which results in further restriction of blood flow and even complete vascular occlusion causing placental ischemia and infarction (Figure 2).

Ivo Brosens has recently [1] linked the degree of spiral artery disease in the placental bed to the different UPVS, with: PTD, PROM and IUGR having only partial failure of *physiological change*; PE having absence of *physiological change*; PE with IUGR, placental abruption and placental infarcts with fetal death, having absence of *physiological change* with obstructive lesions (*acute atherosis*). The current two stage
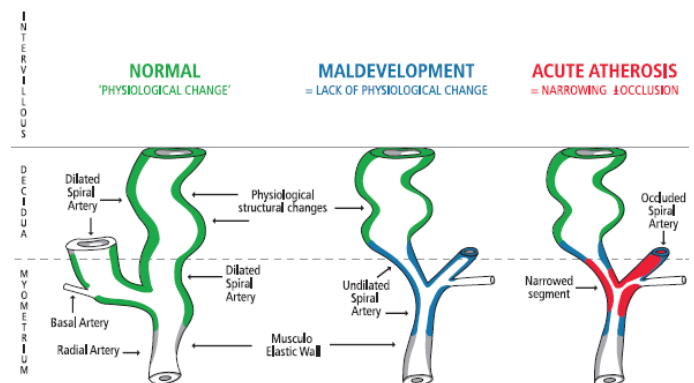

Figure 2. Placental bed spiral artery normal mid-trimester development (of a low resistance circulation - green), maldevelopment (blue) and disease (red)

model for PE of: 1. the vascular stage; 2. the clinical stage [23]; this staging would also apply to all the UPVS.

UPC doppler studies

It was just over 35 years when Stuart Campbell strapped to the side of his real-time ultrasound probe a Doppler ultrasound probe [24]. The probe and its device produced not only sound but also a two-dimensional flow velocity waveform (FVW). From the uterine artery waveforms, he was able to detect abnormal patterns indicative of higher resistance in the UPC in mid-pregnancy. Almost half in this study had pregnancies with subsequent abnormal outcomes had abnormal mid-trimester UAFVW's.

Soon after color Doppler ultrasound machines were developed that allowed it relatively easy to visualise the uterine arteries and produce a UA FVW through the one probe. Subsequently, we [25] and many others were able to confirm Campbell's initial findings and go on to more clearly describe the pathogenesis of the UPVS. But there are at least two features of the UAFVW's in the second trimester that indicate increased resistance: 1. the numerical indices: systolic/diastolic ratio (S/D ratio); Resistance Index (RI); Pulsatility Index; 2. the early diastolic notch (EDN). Both have clinical utility. I prefer S/D ratio as it is the simplest to understand what is being measured. The EDN has been measured as present or absent and some have attempted to quantitated it [26-29], and we have attempted to computerise it [30].

Combining both the both the indices of flow and the EDN is probably the way forward, as we have attempted [31]. Most have accepted the UAFVW from the side showing the highest resistance gives the most useful information in the second trimester. More research needs to be done to better define abnormality in the UAFVW's in the mid-trimester and we hope to do this with the data from the nuMoM2 study [32].

The degree of "***wavy-ness***" of the UAFVW equates with its degree of abnormality. In the analysis of the nuMoM2b study data, we will use a Wavyness Index (WI) of:

WI = S / D X notch depth

WI would then be used to analyse the patterns for the different UPVS.

Biomarkers

Cell-free fetal DNA (cffDNA)

CffDNA has been found to be elevated in patients with PE, with the elevation in cffDNA being proportional to the severity of the

Tensol cast of part of the placenta showing spiral arteries (red) entering the centre of the fetal lobules. (Fetal arteries white)

Circulation of maternal blood in through the intervillous space in relation to the fetal lobular pattern. Density of stippling indicates density of fetal villi.

Figure 1. From Wigglesworth [21]

disease [32]. Levine *et al.* [33] in a prospective series of 120 cases and 120 controls demonstrated that in the 3 weeks before delivery the cffDNA levels in the maternal serum of PE patients rose to more than twice the levels in the controls. They also demonstrated a two-stage elevation of cffDNA in the maternal serum before the onset of PE. The first significant elevation of cffDNA occurred at the end of the second trimester and the second elevation occurred in the last few weeks prior to the development of PE (above). These two peaks in cffDNA are synchronistic with the maldevelopment of the UPC of patients who develop PE, i.e. the failure of physiological change and the development of *acute atherosis*. We have recently communications as to the role of cffDNA in the pathogenesis of PE [34].

It has been hypothesised that the cffDNA levels rise in the maternal blood, primarily from the syncitotrophoblast. The trophoblast is injured by the narrow (undilated) spiral arteries having a *'jet-hose' effect* [35] with associated turbulence.

α-fetoprotein (AFP)

Raised AFP level was the first bio-marker to be found to be associated with UPVS [36]. The raised AFP has been found to be associated with increased numbers of fetal red blood cells in the maternal blood, thus being caused by leaking of fetal blood into the maternal blood from placental villi. The villous injury being also caused by the *'jet-hose' effect* and associated turbulence (above).

Placental Growth Factor (PlGF)

Lowered PlGF has been studied throughout pregnancy and found to have some clinical utility in all trimesters [10]. The PlGF is associated placental size and so a lower level is an indicator of a smaller functioning placenta due to the reduced UPC.

Combining Doppler and biomarker data into an index of risk of UPVS could look like:

UPVS Index = WI *X* AFP (ng/ml) / PlGF (pg/ml) *X* 10

Other bio-physical makers

First trimester uterine artery Doppler studies combined with biophysical and biochemical maternal markers have been shown to predict PE associated with PTD and other UPVS with a modest degree of success [10]. Many attempts have been made to detect other changes in the maternal physiology prior to the clinical manifestation of PE, one of the earliest was ours looking into rising uric acid blood levels and changes in platelet parameters of number and size [37,38]. Most other markers of the clinical stage of PE and other UPVS, have been described which can change before the UPVS clinically manifest but they only predate the UPVS by a few weeks at most (eg. sFlt-1 [39])

Last year, the recommendation statement from a US Preventive Services Task Force (USPSTF) on the screening for PE, was: "to measure the blood pressure throughout pregnancy" [40] – nothing more! Thus, the USPSTF was unimpressed all biomarkers, even proteinuria!

Oxidative stress and the two stages of PE

Why does *'acute atherosis'* develop in some spiral arteries with failed *'physiological change'* with further serious consequences for mothers and infants and not in others? The two stages of PE with the first vascular phase (above) and the second clinical phase. Redman and Sargent [23] described the change as due to oxidative stress and inflammation but the inflammation could just be a result of the oxidative stress. Roberts and Huble [41] questioned whether oxidative stress were not the link

between the two. I hypothesised [35] that the radical oxygen species (ROS) that cause oxidative stress were generated in the maternal liver the enzyme xanthine oxidase – the pathological isoenzyme of xanthine oxidoreductase (XOR) with xanthine dehydrogenase (XDH) non-toxic isoenzyme. The difference is probable genetic and may be nothing more complicated than Mendelian inheritance the gene for activation of XO being recessive and that for XDH being dominant. I have recently communicated on oxidative stress in PE [42], and proposed that ROS are the toxins of Toxaemia of pregnancy [43].

The oxidative stress versions of the stages of PE are thus:

1. Vascular stage; Intracellular (hepatocyte) oxidative stress;

2. *Acute atherosis* and clinical disease manifestation stage: were both are caused by intravascular oxidative stress when the ROS are released from the hepatocytes.

Prophylactic therapy

There is much confusion in this area because of conflicting reports.

Aspirin

Aspirin is effective at delaying the onset of PE [10] but there is confusion about when the therapy should be started with two meta-analyses recently published in the same edition of *American Journal of Obstetrics and Gynecology* [44,45], disagreeing as to whether it should be started before 16 weeks gestation or later. All agree about the pathophysiology of a maldeveloped UPC, then if the failure of the *normal physiological change* that occurs mainly between 14 and 24 weeks gestation, it seems unreasonable to believe the aspirin MUST be started before 16 weeks unless it can be shown that aspirin assists the trophoblast invasion of the spiral arteries by some, as yet undescribed, mechanism and no such evidence exists. Also, those who *'draw a line in the sand'* at 16 weeks, have themselves shown that the PE returns after the aspirin therapy is stopped [10]. Clearly the aspirin therapy does not stop the maldevelopment of the uteroplacental circulation and our retrospective study of mid-trimester UA Doppler would confirm this [46].

Many studies, including ours [47] in meta-analysis [48] have shown that aspirin therapy started after 16 weeks delays the onset of / prevents PE. Is low-dosage of aspirin prophylaxis really necessary: Buffered aspirin in 300 – 325mg dose (Alka-Seltza^R, Bayer, first marketed in 1931) can be taken, one effervescent tablet, twice weekly. As platelet life span is 10 days, at a dose of twice per week only a maximum of only 35% of platelets would ever be active [49].

Antioxidants

The original and RCT of vitamins C and E in 'high risk' patients [8] showed a benefit in preventing PE where high risk was mainly defined as abnormal early mid-trimester UA Doppler studies. In subsequent studies were not of truly high risk patients as they were selected mainly on past history and biophysical profile. They did not show any benefit from the vitamins thus subsequent meta-analyses did not show any benefit but they were not comparing like with like.

Aspirin as an antioxidant / free radical scavenger: There is nothing in obstetrics literature on aspirin as a free radical scavenger and yet other specialities have published on this topic [50]. The obstetrics literature is mainly interested in aspirins inhibition of prostaglandin synthesis and hence its anti-platelet activity. But anti-platelet activity would mainly be useful in the clinical / 'acute atherosis' stage of the disease and aspirin

does not appear to an effect on the loss of 'physiological change' in the spiral arteries (above). As Vitamins C and E are free radical scavenger, for those who discontinue aspirin prophylaxis at 36 to 37 weeks gestation, it could be replaced by these vitamins.

Conclusions:

Uteroplacental vascular syndromes is a better description of these syndromes as 'great obstetric syndromes' and placental ischemic syndromes are not specific as placental ischemia only occurs when there is atherosis of the spiral arteries. In UPVS without atherosis there is reduced placental blood flow and also a 'jet hose' effect from the narrowed (undilated) spiral vessels causing placental injury and increased trophoblast shedding with leaking of fetal blood into the maternal circulation.

UPVS are entities which can be predicted in the first half of pregnancy with UA Doppler flow studies. The predictive ability of UA Doppler will almost certainly improve by combining it with the evaluation of chemical markers, such as cffDNA, α-fetoprotein and/or PlGF.

Outcomes, of many these otherwise normal pregnancies, can be improved with aspirin and / or antioxidant therapies started before twenty weeks gestation. Assessments of both therapies have been confused by contradictory or inappropriate analysis's, confirming my previous criticism of evidence based medicine [51].

Further research needs to be performed to further clarify the pathogenesis and better prediction as well as prophylaxis / treatment of all these UPVS.

In our current state of prenatal testing there is an imbalance of research funding, where the non-invasive prenatal diagnosis (NIPD) for the detection of abnormal foetuses so they can be aborted, heavily outweighs that spent on the detection and treatment of UPVS with their potential for harming and even killing both the mothers and infants who are otherwise normal.

In conclusion to the Conclusion, is a question I proposed 14 years ago; 'Can evidence based medicine be unscientific? [51]'

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