THE “GREAT OBSTETRICAL SYNDROMES” ARE ASSOCIATED WITH DISORDERS OF DEEP PLACENTATION

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Abstract

Defective deep placentaion has been associated with a spectrum of complications of pregnancy including preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion and abruption placentae. The disease of the placental vascular bed that underpins these complications is commonly investigated with targeted biopsies. In this review, we critically evaluate the biopsy technique to summarize the salient types of defective deep placentaion and propose criteria for the classification of defective deep placentaion into 3 types based on the degree of restriction of remodelling and the presence of obstructive lesions in the myometrial segment of the spiral arteries.

Keywords

Spiral artery; physiological transformation; placental vascular bed; adverse pregnancy outcome

Introduction

It is now well-established that placentation in the humans is associated with unique vascular remodeling. The process of physiological remodeling of the spiral arteries during gestation involves a decidua-associated and a trophoblast-associated stage. Such a process involves the decidual and the junctional zone (JZ) myometrial segments (1,2). Deep placentaion involves nearly complete transformation of the decidual and myometrial segments of approximately 100 spiral arteries. Defective deep placentaion was first described in preeclampsia and intrauterine growth restriction (IUGR) and was characterized by absent or incomplete remodeling of the JZ segment of the spiral arteries (3,4). In recent years, defective deep placentaion has also been associated with other obstetrical syndromes, including late spontaneous abortion (5,6), preterm labor with intact membranes and preterm prelabor rupture of the membranes (PROM) (7,8).

In this review, we critically evaluate the biopsy techniques to assess placental bed vascular pathology, summarize the salient features of defective deep placentaion associated with...
different obstetrical syndromes and propose a new classification that we hope will contribute
to a better understanding of the lesions and their pathophysiology.

The study of the placental bed: the beginning

The study of the placental bed began in the late 1950s by two independent groups of
investigators using different biopsy techniques. Dixon and Robertson (9), working in
Jamaica, obtained biopsies at the time of cesarean delivery using biopsy forceps. At the time
of hysterotomy, biopsy samples were obtained under direct visualization from the
implantation site after delivery of the placenta. Using curved scissors, the investigators
obtained a disk that was approximately 1 cm in diameter. Renaer and Brosens (10), in
Leuven, Belgium, obtained biopsy samples after vaginal delivery using a sharpened ovum
forceps. The transvaginal technique required the manual localization and removal of the
placenta to sample the placental bed. Although the placenta wall peeled away from the wall,
the ovum forceps was guided between the palm of the hand and the uterine wall, and a large
biopsy including decidua and a few millimeters of the underlying myometrium was
obtained. In other studies, different techniques have been used to obtain placental bed biopsy
samples. These techniques result in samples in variable size, depth and origin.

Robertson et al. (11) recommended orienting the biopsy so that perpendicular sections of the
decidua and myometrium could be obtained. Both groups examined the entire biopsy
specimen by using a serial sectioning technique, 1 section being stained for every 5, 10 or 20
sections of the tissue.

Histological confirmation that the biopsy was derived from the placental bed was based on
1) the presence of trophoblast, 2) adherent villi or 3) transformed spiral arteries. However,
the absence of these markers does not necessarily mean that the placental bed was not
sampled. In IUGR, a small placental bed may affect the success rate of sampling.
Unfortunately, the success rates have not been systematically reported in most studies. This
is desirable as research in the placental bed moves forward.

A key step in the understanding of the placental bed was made when Brosens (12)
systematically studied the placental bed of 14 patients using cesarean hysterectomy
specimens. The uteri were obtained from mothers who had preeclampsia, preeclampsia with
IUGR, chronic hypertension and nephrotic syndrome. In 3 cases, the placenta was in situ,
which aided the precise mapping of the placental bed. However, when the placenta had been
detached, the implantation site was identified by the presence of trophoblast. In one
specimen obtained from a patient with severe preeclampsia and a fetal death at 31 weeks of
gestation, the uterus contained the fetus and placenta in situ. All specimens were processed
according to the histological technique of sectioning the uterus with placenta in situ,
previously described by Boyd and Hamilton (13). The technique allowed tracing of the
radial arteries in the myometrium and then identification of the individual spiral arteries as
they traveled through the placental bed. In each specimen, 10–25 spiral arteries in the
placental bed and a similar number in the non-placental area were examined. In a large
subsequent study of hysterectomy specimens (with the placenta in situ) obtained between 8
and 18 weeks of gestation, Pijnenborg et al. (14–16) examined the transformation of the
spiral arteries during the first half of pregnancy.

The uteroplacental blood supply

Spiral artery remodelling—After the physiological changes of the spiral arteries in the
placental bed were identified, it was postulated that they resulted from the destructive action
of trophoblast on the vascular musculature and the elastic membrane. However, it was soon
observed that changes associated with trophoblast invasion were preceded by edema of the

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wall, disintegration of the elastic elements and changes in smooth muscle cells, such as rounding of the nucleus, the loss of myofibrils and dense bodies and accumulation of glycogen (17).

Subsequent investigation of hysterectomy specimens between 8–18 weeks that were studied by Pijnenborg et al. (14, 16) resulted in 2 major findings. First, vascular changes that included disorganization of the muscular wall could not be exclusively attributed to the presence of trophoblast. It was noted that vascular smooth muscle became disorganized before the arrival of endovascular trophoblast; however, this disorganization was enhanced in the presence of interstitial trophoblast. The second finding was the apparent occurrence of endovascular invasion in the JZ myometrium. This was considered the second “wave” of trophoblast invasion, which occurred after a 4-week period of trophoblast within the decidua. Although the “two-wave concept” is not accepted universally (18, 19), it provided a valuable model to consider the possible mechanisms responsible for defective deep placentation.

A key question has been the relative contribution of the trophoblast and the decidua in vascular remodeling of the spiral arteries. Craven et al. (20) compared the histological characteristics of spiral arteries in the secretory phase of the menstrual cycle using endometrial biopsy specimens and decidual arteries from patients who underwent elective termination of pregnancy. They concluded that the initial stages of physiological change of the spiral arteries occurred without evidence of trophoblast invasion. However, King and Loke (21) noted that “fibrinoid necrosis” of the wall does not occur in the absence of trophoblast invasion. Kam et al. (22) compared the blood vessels from the implantation sites of early human pregnancies with specimens in which trophoblast was absent. The results confirmed that true physiological transformation of the spiral arteries occurred only in the presence of trophoblast. Recently, Smith et al. (23) examined samples of the decidua basalis (8–12 weeks of gestation) using immunohistochemistry, and provided evidence that uterine natural killer cells and macrophages participate in the remodeling through the induction of apoptosis or extracellular matrix degradation. They also reported that in the early stages of spiral artery remodeling, vascular smooth muscle cells showed dramatic disruption and disorganization preceding the presence of endovascular trophoblast.

Deep placentation

Two major factors determine the maternal blood flow to the placenta. The first is the size of the placental bed, which is determined by the number of spiral arteries that communicate with the intervillous space. In a study that was undertaken to reconstruct the basal plate of the placenta of normal patients, Brosens and Dixon (24) described an irregular distribution of the arterial openings in the intervillous space. They found that arterial openings frequently clustered in groups of 2 or 3 and were located in close proximity to the placental septa (Figure 1). In a careful and detailed study, 48 arterial openings of the spiral arteries were counted (the total was estimated to be 120 openings, based on the examination of a specimen that represented two-fifths of the basal plate). It was also found that each opening corresponded to 1 spiral artery with a density of one artery per 2cm² of basal plate. Serial sections of hysterectomy specimens demonstrated that the radial arteries were divided approximately 0.5 cm beneath the endometrium (i.e. myometrial JZ) into 2 or 3 arteries with physiological changes or transformation. This may explain the clustering of 2 or 3 openings of spiral arteries in the intervillous space (Figure 1).

A second feature in determining maternal blood flow to the placenta is that the depth of spiral artery physiologic transformation is greater in the center of the placental bed than in the periphery (15, 16). This is consistent with the observation that the degree of trophoblast invasion is less in the periphery than in the center of the placental bed. Indeed, interstitial
trophoblast is absent or scanty in the periphery, and physiologic transformation of the myometrial segment of the spiral arteries is partial or absent, even in normal pregnancy (Figure 1). However, such phenomenon involves approximately 10% of the spiral arteries of the placental bed (12, 24).

Placental bed biopsy studies confirm most of the spiral arteries show full transformation in the JZ myometrial segment (Table 1; Figure 2A). These findings are consistent with the observation reported from ultrasound studies. Color and pulsed-Doppler studies performed during the second trimester of pregnancy have demonstrated a lower impedance to blood flow in the central area of the placental bed than in the periphery (30).

Defective deep placentation
Defective deep placentation is characterized by a significantly increased number of JZ myometrial spiral arteries with absent or partial transformation (Figure 2B and 2C). Physiologic transformation of the spiral arteries is not an “all or none” phenomenon (31). We have noted that there is some confusion in the literature about the definition of partial transformation (5, 27, 32). An objective assessment of the degree of physiological changes may be achieved by calculating the proportion of the artery that is transformed (31).

In severe preeclampsia, only a few spiral arteries in the center of the placental bed may show full transformation of the JZ myometrial segment (Figure 3). In addition, obstructive arterial lesions (e.g. thrombosis, acute atherosis) may develop and contribute to the severity of defective deep placentation (Figure 2D).

Although the distribution of interstitial trophoblast in the JZ myometrium is not homogeneous (and varies not only between patients, but also between biopsy specimens from the same patient), placental bed biopsy specimens have limitations because they only provide information about a small segment of the placental bed. It is possible that areas close to the nonbiopsy site may have a completely different degree of vascular transformation (15).

Obstetrical syndromes associated with defective deep placentation
More than 50 years after the original observations, it has become clear that disorders of deep placentation occur in a broader range of clinical complications of pregnancy than initially thought. This underscores the importance of this disorder because it is present in virtually every major obstetrical syndrome.

Preeclampsia
The placental bed of patients with preeclampsia is characterized by a decreased number of spiral arteries with transformation of the myometrial segment (Table 1; Figure 2C). This segment retains a hypertrophic muscular structure, although interstitial trophoblasts are present, sometimes in excessive numbers (3). The defective transformation is more severe in the myometrial, than in the decidual, segments (8, 29).

Preeclampsia with IUGR
The placental bed of patients with preeclampsia associated with IUGR is similar to that described in patients with preeclampsia. It is characterized by a large number of nontransformed myometrial spiral arteries, and such arteries show frequently obstructive lesions, such as acute atherosis and thrombosis (33, 34) (Table 2; Figure 2D). Acute atherosis was first described by Zeek and Assali (35) not only as a distinctive disorder of small decidual arteries, but is also a prominent lesion of the myometrial spiral arteries in cases of preeclampsia with IUGR (33, 34). Defective deep placentation in preeclampsia with
IUGR results in a small central region with transformed arteries, as demonstrated by hysterectomy specimens with the placenta in situ (36, 37) (Figure 3). The extent of defective transformation of myometrial spiral arteries and the presence of obstructive myometrial vascular lesions explain the frequent association with placental infarctions.

**Intrauterine growth restriction without hypertension**

In placental bed biopsy studies of pregnancies complicated by IUGR, Brosens et al. (34) described in 1977 (in the absence of maternal hypertension) that 55% of the biopsies showed absence of physiological changes in the myometrial segment of the spiral arteries, while no physiological changes were seen in 23 biopsies from women with preeclampsia with or without IUGR. In this condition, partial transformation of the myometrial spiral arteries has been reported by other investigators (5, 25, 38). Khong et al. (5) reported absence of spiral artery remodeling at the level of the decidual segments in women with IUGR without hypertension and indicated that the lack of physiological change may also be confined to part of the circumference of the vessel with the remaining portion of the circumference showing normal remodeling.

**Preterm labor and preterm PROM**

*Preterm labor and preterm PROM* are defined as events that occur at <37 weeks of gestation and can be considered as 2 syndromes with various phenotypes. Multiple etiologies include infection/inflammation, ischemia due to vascular disease, cervical disease, uterine overdistension, abnormal alloagraft reaction, allergy, and endocrine disorders. (39).

In a blinded cross-sectional study, Kim et al. (7) determined the frequency of nontransformed spiral arteries in placental bed biopsy specimens obtained under direct visualization at the time of cesarean delivery in three groups of patients: 1) normal women who delivered at term; 2) patients with preterm PROM who underwent cesarean delivery for obstetric indications; and 3) patients with preeclampsia.

The frequency of failure of physiological transformation of the myometrial segment of the spiral arteries was significantly higher in patients with preterm PROM than in patients who delivered at term. Completely transformed spiral arteries were observed in 59% of patients who delivered at term, 29% of those with preterm PROM, and 4.3% of patients with preeclampsia. Interestingly, the authors observed that preeclampsia had a higher mean number of vessels with defective physiologic changes in the decidual portion than in preterm PROM. They interpreted these observations to suggest that the placentalation disorder in preeclampsia (which consistently involves the decidual and myometrial segments) is more severe and probably begins earlier in gestation than the one observed in cases of preterm PROM.

In a similar systematic study, Kim et al. obtained placental bed biopsy specimens at the time of cesarean delivery in patients with preterm labor with intact membranes who had a preterm delivery (8). The study included a control group of women with normal pregnancy and a group of women with preeclampsia. The authors observed that patients with preterm labor with intact membranes who delivered a preterm neonate had a greater degree of failure of transformation of the spiral arteries in the myometrial and decidual segments than women who delivered at term. However, the extent of this defect was much greater in patients with preeclampsia than in those women with preterm labor with intact membranes.

**Abruptio placentae**

Dommisse and Tiltman (40) reported the results of placental bed biopsy specimens that had been obtained at the time of cesarean section delivery in 18 women with the clinical
diagnosis of abruptio placentae. Six biopsies did not include trophoblast in the myometrium and therefore were not considered representative of the placental bed. In 12 cases, at least one spiral artery was seen in the myometrium. Seven of the 12 specimens demonstrated absence of physiological transformation of the spiral arteries. Hemorrhage was observed in 83% of these samples. Brosens (12) reported that 65% (15 of 23 spiral arteries) of non-transformed spiral arteries were affected by acute atherosis in a cesarean hysterectomy specimen from a patient with hypertension and abruptio placentae.

**Second trimester abortion**

In a preliminary study, Khong et al. (41) described that failure of physiological transformation of the spiral arteries could be observed in women with a spontaneous abortion in the mid trimester. Ball et al. (6) subsequently reported a large series of placental bed biopsy specimens that contained myometrium from late spontaneous abortions from women who had undergone karyotype. The placental implantation site was determined with ultrasound scanning before the termination of pregnancy. A biopsy forceps was introduced through the cervix, and placental bed biopsies were performed under ultrasound visualization (3 or 4 placental bed biopsy specimens of 3–5 mm³ were obtained). When compared with normal pregnancies, myometrial spiral arteries of patients with a second-trimester abortion (late fetal death) showed reduced endovascular and intramural trophoblasts and less extensive fibrinoid deposits in the wall of the spiral artery. Of interest was that the amount of endovascular trophoblast in the decidual segment of the spiral arteries was increased. However, the extent of interstitial trophoblast in the myometrial segment was not significantly lower in patients with a spontaneous abortion. Endovascular trophoblast invasion may become arrested at the decidual level and fail to progress into myometrial segment of the spiral artery. Additionally, musculo-elastic tissue did not persist in myometrial spiral arteries, which suggested that physiological changes may not be entirely dependent on trophoblast invasion. However, it cannot be excluded that a weakening of the elastic layer may be induced by interstitial trophoblast (42).

**Comment**

Defective deep placentation is associated with a spectrum of obstetrical syndromes that included preeclampsia, IUGR, preterm labor with intact membranes, preterm PROM, abruptio placentae and spontaneous mid trimester abortion. We propose that disorders of deep placentation are characterized by: 1) the degree of restriction of physiologic transformation of the spiral arteries and 2) the presence of arterial lesions in the JZ myometrium of the placental bed.

The degree and extent of physiologic transformation of the spiral arteries varies according to the area of the placental bed and is less in the periphery than in the central part of the placental bed. In normal pregnancy, 90% of the JZ myometrial spiral arteries are fully transformed (Figure 4A).

Three different types of defective spiral artery transformation can be identified in the JZ myometrium: 1) partial transformation; 2) absence of transformation; and 3) absence of transformation with obstructive lesions (Table 3). In preeclampsia, complete physiologic transformation of the spiral arteries in the JZ myometrium is greatly reduced in the central area of the placental bed (Figure 4B). In preeclampsia associated with IUGR, defective deep placentation is frequently observed with the presence of obstructive lesions in the non-transformed myometrial spiral arteries. In preterm labor and IUGR without hypertension, the defective deep placentation may affect only partially affect the spiral arteries in the JZ myometrium.
Spiral artery remodeling has been described as a multistep process that starts at the beginning of pregnancy (43). Based upon histological studies of well-timed early pregnant hysterectomy specimens and numerous third-trimester placental bed biopsies, 4 steps have been distinguished in the spiral artery remodeling: 1) the initial stage of decidua-associated remodeling is followed by 2) intra-arterial trophoblast migration, 3) intramural invasion and trophoblast-associated remodeling, and 4) reendothelialization and other maternal-induced changes. Although the precise mechanisms of defective remodeling are not known, it seems logical to assume that different clinical conditions can lead to various defects of transformation and result in different types of defective deep placentation. Kim et al. (7) interpreted the association of partial transformation with preterm delivery and preterm PROM to suggest that the placentation disorder in preeclampsia is more severe and may begin early in gestation.

Brosens et al (44) recently suggested that the process of cyclic decidualization, followed by menstruation serves as a mechanism to prepare the uterus for deep placentation. Both menstruation and implantation are inflammatory conditions that cause some physiological ischemia-reperfusion tissue stress, albeit much more so in pregnancy. The authors speculated that the emergence of cyclic menstruation may have had a critical role in protecting uterine tissues from the profound inflammatory and oxidative stress associated with deep placentation, a process known as “preconditioning”. In addition, it is interesting to note that normal pregnancy-induced fragmentation of the internal elastic lamina of the myometrial spiral arteries persist following a first pregnancy (45), which could provide an anatomic explanation for higher birthweight in the second and subsequent pregnancies.

The absence of adequate “preconditioning” may explain why pregnancy in the early teenage primigravida women is associated with a significantly increased risk of poor pregnancy outcomes, such as preterm delivery, fetal growth restriction and preeclampsia in comparison with primigravidae women in their early twenties, in whom preconditioning has occurred (46). On the other hand, placentation disorders, even during the subclinical stages, are present in a subset of patients with preeclampsia and fetal growth restriction. Under these circumstances, defective deep placentation is characterized by non-transformed JZ spiral arteries that can be affected severely by obstructive vascular lesions. Arterial lesions such as intimal hyperplasia, acute atherosis and thrombosis can develop in these arteries over a surprisingly short period of time, even with mild hypertension.

The association of obstetrical syndromes with different vascular diseases in the JZ myometrium suggests that the preconditioning of this zone at the time of conception may be critical factor for successful implantation and development of normal placentation. Romero et al. (47) have proposed that more than one mechanism of disease may lead to defective deep placentation and that the common pathophysiologic consequence is ischemia. The extent and timing of ischemia as well as the host response (maternal and fetal) would lead to different clinical phenotypes. Genetic and environmental factors, as well as the time of onset, duration and extent of the ischemic insult, may play a role in the determination of the phenotype. Recently, Roberts and Hubel (48) arrived at a similar conclusion and proposed that factors that increase the risk for preeclampsia are also associated with abnormal implantation.

Progress in understanding the molecular processes that occur during implantation indicates that, among other maternal constitutional factors, the process of endometrial decidualization and angiogenesis is a target for pre-pregnancy diagnosis and therapy. Therefore, the characterization of angiogenesis and the development of biomarkers in early placental development are likely to provide diagnostic and hopefully noninvasive predictive markers to identify mothers at risk for defective deep placentation syndromes such as preeclampsia.
(49–61), IUGR (62–65), preterm birth (66, 67) and other adverse pregnancy outcomes (68–74).

A proper classification of defective deep placentation also has important implications for fetoplacental research and the diagnosis of placental disease by imaging techniques. Although a placental biopsy specimen may not be representative of the entire vascular placental bed, some authors have attempted to standardize the technique by using ultrasound scanning to target biopsies from the center of the placental bed (28). This technique may reduce the failure rate, but would not address the presence of lesions and their severity in the paracentral region. Similarly, color Doppler and spectral Doppler ultrasound studies of spiral arteries also have limitations, because they do not address the lateral extent of spiral artery remodeling. This means that the conclusions reached with such noninvasive studies should be interpreted with caution (75, 76).

The “Great Obstetrical Syndromes” (77, 78) are associated with defective deep placentation, which may be associated with different degrees of restricted remodeling and obstructive lesions of the spiral arteries in the JZ or inner myometrium. This concept may be used to improve the characterization of the disorders of the placental bed. It is possible that this information will be valuable in refining the existing tools for the assessment of risk before pregnancy outcome.

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References


Figure 1.
Figure 2.
Spiral artery in the junctional zone myometrium showing: full transformation characterized by the loss of musculo-elastic structure and the presence of fibrinoid with cytotrophoblast (A), partial transformation (top and right) (B), absent transformation (note trophoblastic giant cells surrounding the artery) (C) obstructive lesions by acute atherosis and intimal hyperplasia and absence of transformation and (D) PAS staining, highlighting the fibrinoid in A and B. Brosens. Morphological changes in the utero-placental bed in pregnancy hypertension. Clin Obstet Gynaecol 1977.
Figure 3.
Figure 4.
A. Normal placental bed with full transformation of the myometrial spiral arteries except at the periphery of the placental bed B. Defective deep placentation is characterized by non-transformation of the myometrial spiral arteries reducing the central area with deep placentation.
Table 1
Remodeling of myometrial segment in normal pregnancy versus preeclampsia in placental bed biopsy studies

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<tr>
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<th>Normal</th>
<th>Preeclampsia</th>
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<tr>
<td>Gerretsen (25)</td>
<td>22/23 (96%)</td>
<td>1/30 (3%)</td>
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<tr>
<td>Khong (5)</td>
<td>18/18 (100%)</td>
<td>3/14 (21%)</td>
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<tr>
<td>Frusca (26)</td>
<td>13/14 (93%)</td>
<td>6/24 (25%)</td>
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<tr>
<td>Meekins (27)</td>
<td>16/21 (76%)</td>
<td>3/24 (12%)</td>
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<td>Sagot (28)</td>
<td>16/20 (80%)</td>
<td>7/17 (41%)</td>
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<tr>
<td>Kim (7)</td>
<td>55/59 (93%)</td>
<td>9/31 (29%)</td>
</tr>
<tr>
<td>Kim (8)</td>
<td>89/103 (86%)</td>
<td>18/43 (19%)</td>
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<tr>
<td>Guzin (29)</td>
<td>16/20 (80%)</td>
<td>11/32 (33%)</td>
</tr>
<tr>
<td>Mean</td>
<td>88%</td>
<td>27%</td>
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<tr>
<td>Range</td>
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### Table 2

Obstructive lesions in myometrial segment of placental bed spiral arteries in hysterectomy specimens (12)

<table>
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<tr>
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<th>Cesarean hysterectomy n</th>
<th>Arteries with obstructive lesions n (%)</th>
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<tr>
<td>Normotensive</td>
<td>8</td>
<td>0/103 (0%)</td>
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<td>Chronic hypertension</td>
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<td>0/24 (0%)</td>
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<tr>
<td>Preeclampsia</td>
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<td>3/27 (8%)</td>
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<tr>
<td>Preeclampsia with IUGR</td>
<td>2</td>
<td>23/33 (70%)</td>
</tr>
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</table>

IUGR: intrauterine growth restriction
### Table 3

Types of defective deep placentation in association with adverse pregnancy outcomes

<table>
<thead>
<tr>
<th>Type of myometrial spiral artery remodeling</th>
<th></th>
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<tr>
<td>Partial</td>
<td>Preterm labor</td>
<td></td>
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<tr>
<td></td>
<td>Preterm PROM</td>
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<tr>
<td></td>
<td>IUGR without hypertension</td>
<td></td>
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<tr>
<td>Absent</td>
<td>Preeclampsia</td>
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</tr>
<tr>
<td>Absent with obstructive lesions</td>
<td>Preeclampsia with IUGR</td>
<td></td>
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<td></td>
<td>Abruptio placentae</td>
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PROM: premature rupture of membranes; IUGR: intrauterine growth restriction