Spiral Arteries in Second Trimester of Pregnancy: When Is It Possible to Define Expected Physiological Remodeling as Abnormal?

Mercedes Olaya-C [1] · Marta Garrido [2] · Jorge Andrés Franco [3] · Jorge Luis Rodríguez [1] · Magda Jimena Vargas [1] ·
Ana Aula-Olivar [2] · Laura Quintero [4] · Santiago Ramón y Cajal [2,5,6]

Abstract

After undergoing remodeling, uterine spiral arteries turn into wide, flexible tubes, with low resistance. If remodeling does not occur, spontaneous abortions, intrauterine growth restriction, and pregnancy-related hypertensive disorders can ensue. Arterial transformation begins at a very early gestational stage; however, second quarter pregnancy histopathological samples have yet to pinpoint the exact moment when abnormal remodeling transpires. We examined 100 samples, taken from consecutive abortions at 12–23 gestational weeks. Following Pijnenborg and Smith guidelines, blinded pathologists analyzed clinical data on remodeling stages. Lab results showed that arterial remodeling is not synchronic in all vessels; a single sample can include various remodeling stages; neither is remodeling homogenous in a single vessel: change may be occurring in one part of the vessel, but not in another. To our knowledge, no one has published this finding. In the examined age group, Smith stage IV predominates; around week 14, substantial muscle and endothelium loss takes place. After week 17, endovascular or fibrin trophoblast does not usually occur. Although scant consensus exists on what defines preeclampsia etiology, it is clear that it involves abnormal remodeling in decidua vessels. Improved understanding requires further knowledge on both the physiological and pathological aspects of the remodeling process. We observed that muscle and endothelial tissues disappear from weeks 14–17, after which time reendothelization predominates. We list the expected proportion of spiral artery changes for each gestational age which, to date, has not been available.

Keywords Spiral arteries · Vascular remodeling · Endovascular trophoblast · Trophoblast invasion · Preeclampsia

✉ Mercedes Olaya-C
olaya.m@javeriana.edu.co; molaya@husi.com

Marta Garrido
magarrido@vhebron.net

Jorge Andrés Franco
jafrancoz@javeriana.edu.co

Jorge Luis Rodríguez
jlrodriguez@javeriana.edu.co

Magda Jimena Vargas
magda_vargas@javeriana.edu.co

Ana Aula-Olivar
Aaula@vhebron.net

Laura Quintero
quintero_laura@javeriana.edu.co

Santiago Ramón y Cajal
sramon@vhebron.net

[1] Department of Pathology, Facultad de Medicina, Institute of Human Genetics, the Medical School, Pontificia Universidad Javeriana-Hospital Universitario San Ignacio, Kra 7a 40-62, Bogota, Colombia

[2] Pathology Department, Vall d'Hebron Hospital, 08035 Barcelona, Spain

[3] Department of Morphology, Facultad de Medicina, Pontificia Universidad Javeriana, Kra 7a 40-62, Bogota, Colombia

[4] Facultad de Medicina, Pontificia Universidad Javeriana, Kra 7a 40-62, Bogota, Colombia

[5] Translational Molecular Pathology, Vall d'Hebron Research Institute (VHIR), Universitat Autónoma de Barcelona, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain

[6] Spanish Biomedical Research Network Center in Oncology (CIBER ONCnc), Barcelona, Spain

Introduction

A fetus receives adequate nutrients and oxygen during gestation thanks to an increase in maternal blood flow brought about by physiological changes that lower resistance in arteries [1]. Vascular decidua remodeling transforms small muscular arteries into distended flaccid vessels [2]; abnormal vascular remodeling has been linked to spontaneous miscarriage, intrauterine growth restriction, and hypertensive disorders of pregnancy (HDP), mainly preeclampsia [2–7]. Although researchers have yet to reach a consensus on preeclampsia etiology, they do agree that vascular remodeling is abnormal [1, 2, 8–11]. This process begins very early during pregnancy; however, according to most sources, the second trimester is when major changes take place [12]. Nonetheless, pathologists have not designated a specific period when incomplete, delayed, partial, absent, or deficient remodeling takes place in relation to gestational age. Some authors consider the process to be abnormal if by week 20 it is not complete [13]; however, most studies on this gestational process have been carried out only after delivery [7]. Furthermore, any of these arterial irregularities could indicate a "bad start" early in pregnancy and lead to diagnosis of "abnormal arterial remodeling." Although preeclampsia is not clinically discernable prior to week 20, it has undoubtedly already begun in maternal vessels. Therefore, detecting the clinical moment when abnormal maternal vascular remodeling occurs is critical since it is related to IUGR and other autoimmune diseases that often show up in the second trimester of pregnancy and lead to fetal death.

The remodeling process comprises simultaneous loss of the endothelium and of smooth vascular muscle cells that are then replaced by endovascular trophoblasts (vEVTs) embedded in the fibrinoid [14]. Consequently, extravillous trophoblasts located in the tip of the anchoring chorionic villi proliferate early in pregnancy [2] and invade the uterine wall and maternal arteries [15, 16]. Prior to this, decidual NK (dNK) cells and macrophages apparently pave the way for the trophoblast invasion [7]. At the onset of gestation, when the trophoblast invasion, stimulated by maternal hypoxia, takes place [17], the roles of extravillous trophoblasts as invasive endovascular or interstitial trophoblast are being defined. Endovascular trophoblast cells should replace the endothelium, and interstitial trophoblast cells should be situated between the vasculature [18]; both kinds of trophoblasts work together in vascular remodeling [19]. At gestational week 10, less than 5% of myometrial arteries exhibit endovascular extravillous trophoblasts, but at weeks 16–18, the described percentage rises to 32% [20]. Trophoblast cells replace the endothelium in the spiral arteries, specifically in decidual portions [21]. Persistent endothelium and prenatal abnormalities in endothelial cells are involved in pregnancy complications and in mother's long-term prognosis [22].

We know that a mother who has suffered from preeclampsia is at increased risk of developing preeclampsia again [23].

Using routine pathology samples, this study attempted to focus—whenever possible—on a short period in the second trimester to define normal spiral artery remodeling or to differentiate abnormal types.

Materials and Methods

At the *Vall d'Hebron Hospital*, Barcelona, Spain, we assembled tissue bank samples from one hundred consecutive abortion cases related to either voluntary pregnancy interruptions or spontaneous miscarriages. We limited tissue analysis to paraffin-embedded samples taken at gestational ages between 12 and 23 weeks; for these curettage samples, all mothers had consented; clinical records provided information on main diagnosis and gestational age; clinical variables of interest included mother's age, gestational age, principal diagnosis, and parity. Early ultrasounds (some on date of last menstruation) had calculated most gestational ages. Our main objective in this study was to analyze real human samples sent to pathology labs. When reviewing curettage material, we selected slides containing basal plate, which had highlighted artery features with histochemical markers for elastic fiber including periodic acid-Schiff stain and Masson trichrome stain. We evaluated samples at the Javeriana University San Ignacio-Hospital in Bogota, where the Institutional Medical Research and Ethics Committee approved the collaborative study. Two blinded perinatal pathologists evaluated the samples. Researchers microscopically examined the entire number of arteries. Data collected includes number of arteries from evaluation, stage of remodeling, and each criterion shown in Table 1.

Pijnenborg described five stages of vascular remodeling [4]: the changes involved the endothelium, the muscle cells, the interstitial trophoblast, the endovascular trophoblast, the intramural trophoblast, the fibrinoid layer, and finally reendothelialization. Smith's classification has four states [14]; both classifications are consolidated in Table 2, and both included the same structures. We used a mixture of these two classifications: one classification may describe some findings, while the other may not (Pijnenborg's includes some changes for early stages and has stage V); if the finding was present, then we assigned the stage described in the pertinent classification. We considered spiral artery conversion as *complete* when all arteries observed in the samples displayed changes defined in terms of "dilatation, loss of smooth muscle and reendothelialization" [24]. We defined remodeling as *incomplete* when only some of the arteries exhibited said changes, yet others did not, while at the same time, a certain amount of smooth muscle layer remained within the media, or the fibrinoid or the intramural trophoblast. If the entirety of arteries showed no

Table 1 Demographic features

Variable	N (%)
Twins	
Twin pregnancy	5 (5.10)
Singleton pregnancy	93 (94.90)
Fetal gender	
Male	57 (56.43)
Female	42(43.56)
Without data	2 (1.98)
Maternal age (years), mean 34.5	
< 18	1 (1.02)
18–35	54 (55.10)
> 35	43 (43.88)
Gestational age (weeks), mean 16.7	
12	1 (0.98)
13	8 (7.85)
14	16 (15.68)
15	15 (14.71)
16	7 (6.86)
17	22 (21.58)
18	10 (9.80)
19	2 (1.96)
20	5 (4.90)
21	12 (11.76)
22	1 (0.98)
23	3 (2.94)
Chromosomal disorders	
Triploidy (69,XXY)	1 (0.98)
Trisomy 13	1 (0.98)
Trisomy 18	2 (1.96)
Trisomy 21	17 (17.35)
Pelizaeus-Merzbacher disease/mutation PLP1	1 (0.98)
Turner syndrome (monosomy X)	2 (1.96)
Cri-du-chat syndrome	1 (0.98)
Unbalanced translocation 1:4	1 (0.98)
Nonspecific triploidy	1 (0.98)
Without chromosomal disorder	73 (74.49)
Major malformations	
Genitourinary system	7 (6.86)
Cardiovascular and respiratory system	8 (7.85)
Central nervous system	6 (6.12)
Multiple malformations	4 (4.08)
Bone and soft tissue malformations	7 (6.86)

Regarding multiple pregnancy cases, in some cases, a separate sample was received from each twin, thus contributing two individuals to the study (one case). In other cases, we analyzed a joint tissue sample from two deceased individuals (two individuals provided one sample: two twin pregnancies represented five individuals, because in one case they were triplets); in others, only one twin provided a sample because the other survived (two cases). There are five mothers of twin pregnancies

changes at all, we classified this state as *absence of remodeling.*

In our research, based on a descriptive observational study, we evaluated the association between histological findings and interest groups by calculating raw odds ratio (OR) analysis with 95% confidence intervals (CI); we calculated means and percentages and then summarized the data. We analyzed qualitative variables with absolute frequencies, and extreme or aberrant data in detail in relation to the different variables. The hypothesis test determining p value is Ho, OR = 1, and two-tailed Ha, different from OR 1. Only variables with p value < 0.05 were retained in final statistical models. We performed statistical analysis with Stata 14.2.

We were unable to check myometrial segments or the myometrium of the junction area per se, due to curettage sample characteristics.

Results

We examined one hundred samples selected from the consecutive series of both spontaneous and provoked abortions at 12 to 23 weeks. Table 1 illustrates population characteristics. Sample population was predominately male (56.43%) versus female (43.56%). Gestational age ranged from 14 to 17 weeks. Although we analyzed one hundred cases, abortion tissue samples could have belonged to more than one individual, since we did not exclude multiple pregnancies.

Mothers' ages followed a distinctive distribution pattern: most fell either into the 18–35 years (55.10%) age group or into 35+ years (43.87%). We considered this distribution to be distinctive since, in most gestational series, the older age group usually accounts for no more than a quarter of the population, whereas, in our series, it accounted for nearly half.

We found 26.73% of fetuses with chromosomal disorders and 31.68% with some kind of congenital malformation, predominately cardiovascular and urinary system malformations. Four multiple gestations included three twin pregnancies and one triplet. Only one mother had chronic hypertension, and six had premature membrane rupture. No mother suffered from autoimmune disorders. We found only one case of IUGR. We also encountered other maternal disorders such as endocrine [1], depressive [2], and HIV [1].

Pathological results led to diagnoses for chorioamnionitis (14.3%), retroplacental hematoma (6.1%), single umbilical artery (0.98%), and trophoblast inclusions (18.4%).

Under microscopic examination, arteries revealed extensive variation in number of vessels: 20 cases with less than 5 (20.41%), 46 with 5 to 10 (46.94%), and 32 with more than 10 vessels (32.65%). Figure 1 shows vascular changes according to stages. The most frequent observations involve asymmetric and asynchronous processes that constitute spiral artery remodeling: we often encountered different stages in the same

Table 2 Classification and stages of vascular remodeling, according to Smith [14] and Pijnenborg [4]

Classification and stages of vascular remodeling	Endothelium		Vascular smooth muscle cells			Endothelium	Endovascular trophoblasts	Endothelium	Vascular smooth muscle cells	Fibrinoid	Endovascular trophoblasts	Vascular
	Intact	Vacuolation	Intact	Swelling	Disruption, disorganization, and partial loss	Some breaks	Present in lumen	Substantial loss	Substantial loss	Detected in vessel wall	Present in lumen and relining vessel	Reendothelialization and subintimal thickening
Smith	I	N.A.	I	II	II	II	III	III	III	III-IV	IV	N.A.
Pijnenborg	0	1	0	1	II	N.A.	III	N.A.	IV	IV	IV	V

slide, or even in the same field. Furthermore, in the same blood vessel, we repeatedly observed that on one edge, remodeling changes appeared, whereas on the other edge, a different phase of the process was underway. Figure 2 shows examples of vessels that exhibited this "zipper-like" phenomenon that covers first one side and then the other and which occurs in all stages.

Based on the abovementioned classifications, 73.47% of cases fell within stages II and IV (Fig. 3). Since we encountered asynchrony in the remodeling process for each vessel, we first evaluated percentage of changes and then rated them.

For gestational ages, stage IV predominated and, as pregnancy progressed, constantly became more frequent; however, stages II and III disappeared by week 17. According to our data, no complete remodeling had taken place until week 23.

Histochemical (elastic fiber, periodic acid-Schiff stain, and Masson trichrome stain) studies enhanced the visualization of fibrin, muscle, and elastic fibers; nonetheless, we eventually excluded this step, because H&E sufficed in making proper identification (Figs. 1 and 2). Additionally, since spiral arteries in the decidua are arterioles, they do not have a discernable elastic layer.

Eight cases displayed discordant remodeling for their respective gestational ages (cases with remodeling ahead or behind for their age). In pinpointing them, we carried out a blinded first slide evaluation and then reviewed discordant cases in order to spot registry errors. We further analyzed all cases, searching for risk factors and other variables of interest: we found no discordant remodeling cases related to the presence of malformations, chromosomal disorders (p 0.58, OR 2.8 (CI 0.32–24.39)), advanced maternal age (p 0.72, OR 1.17 (CI 0.15–8.68)), or fetal gender (p 0.72, OR 1.17 (CI 0.18–7.38)). We encountered no differences between spontaneous and non-spontaneous interruptions of pregnancy, nor did number of vessels seem to affect discordant remodeling data. We classified discordant remodeling results into cases with remodeling ahead or behind for age. Note in Fig. 3, for example, the case at 12 weeks whose remodeling we classified as stage IV, or the case at 17 weeks with remodeling classified as stage II.

Discussion

Anywhere from 100 to 150 spiral arteries, ranging from 200 to 300 μm in diameter [2], can be found in the placental bed. Although no specific second trimester data is available, our study showed extensive variation in size and number of arteries.

Because our population's pregnancies frequently resulted in unfavorable outcomes, we termed maternal age distribution as "particular"; furthermore, half of the cases we studied were of those of women over age 35 (10.2% between 40 and
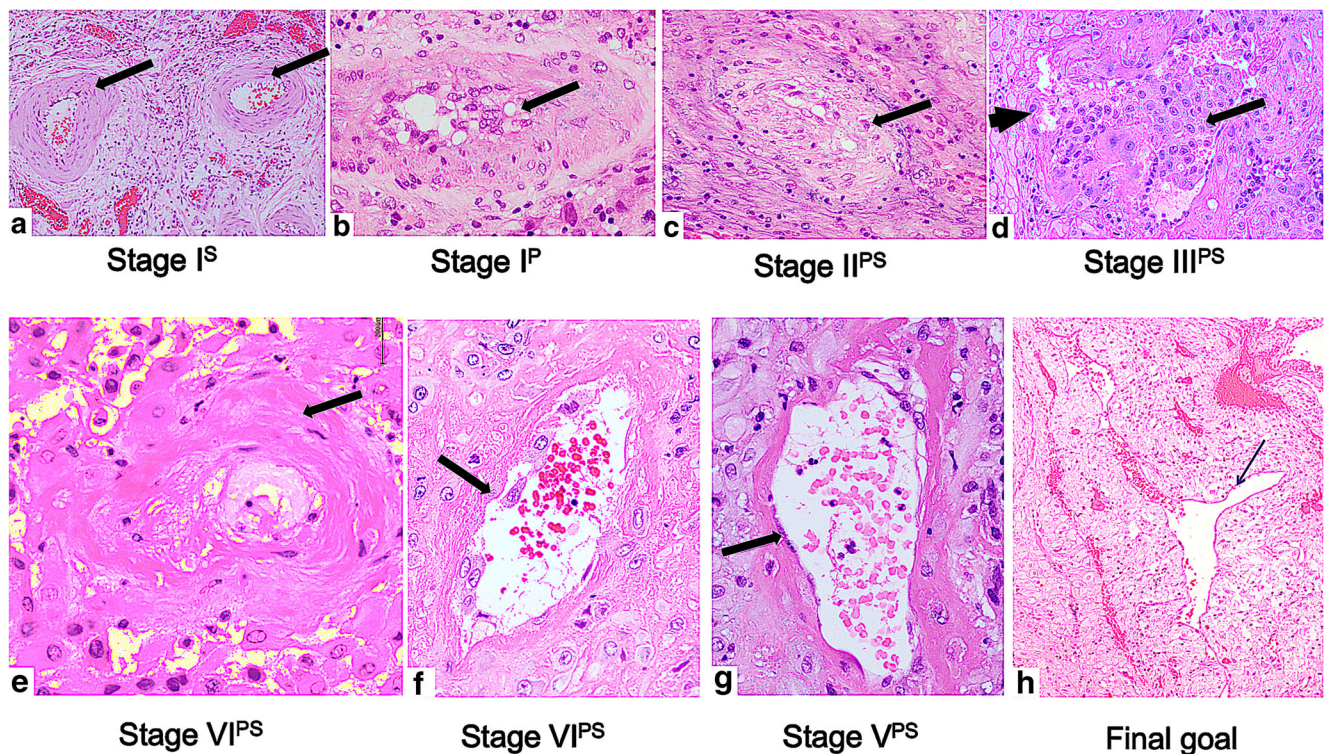
Fig. 1 Vascular changes according to the defined stages. P, Pijnenborg classification; S, Smith classification. **a** Arteries without remodeling. **b** Discontinuous endothelium with edema (arrow). **c** Disordered smooth muscle with rounded nuclei (arrow). **d** Trophoblast present in vascular lumens (long arrow) and lining the vessel wall (short arrow). **e** Fibrin in the vascular wall (arrow). **f** Trophoblast partially lining the wall (arrow). **g** Endothelium reepithelizing the vessel (arrow). **h** Final artery, vena-like (flat endothelium: arrow)

50 years), and 76.7% of fetuses in this cohort suffered from chromosomal disorders or severe malformations. We expected to find differences in the remodeling process in cases with a history of malformations or chromosomal disease, since the literature often describes alterations in the vascularity of the placenta in the presence of chromosomal disorders [25], as it does on the relation between malformations and preeclampsia [26, 27]; however, in our study, we encountered no such deviations. In our study, we observed no morphological differences between normal fetuses and those with chromosomal or formative abnormalities; we found no relation between morphology and the occurrence of such disorders.

As mentioned above, these potential confounders (chromosomal disorders and major malformations) did not appear preponderant at discordant points. Among discordant samples for gestational age, we found no significant differences after comparing samples from fetuses *with malformations* to samples from fetuses *without malformations*. We found the same to be true in older mothers. We also expected to find changes in cases in which these abnormal conditions co-existed, but we found none. Studies based on routine histopathological samples will always pose this problem, since pathology labs rarely analyze normal fetal tissue.

The standard literature on artery remodeling has established that the process starts with a myometrial trophoblast invasion at around gestational ages of 14–15 weeks [7].

As mentioned above, in our study, we collected only the decidual portions of arteries taken from cases as early as gestational age of 13 weeks; in all of them, we observed clear signs of remodeling at gestational age of 13 weeks. This may suggest that the general arterial remodeling process begins earlier than has thus far been suggested.

Although we had insufficient samples of multiple gestations to decisively determine discordant remodeling parameters, we did encounter one case of triplets (at 23 weeks, Fig. 3) with adequate remodeling maturation. All other cases were 18–20-week twins, at stages IV and V (expected). One case of twins with discordant remodeling was a pregnancy at 17 weeks that exhibited stage II remodeling. To sum up, the remodeling process is dynamic and continuous and depends on individual features influenced by fetal and maternal factors [2].

Abnormal remodeling poses a risk not only for the occurrence of preeclampsia—a condition we did not analyze for most of the gestational ages chosen—but also for IUGR and spontaneous abortions [28]. However, due to the lack of study subjects with expected conditions such as IUGR and autoimmune disorders, we were unable to link maternal illness to abnormal artery remodeling. Unfortunately, it is not possible to identify cases that will develop preeclampsia, which should be the main goal of any artery remodeling study. In PE, the persistent smooth vascular muscle, which appears to be
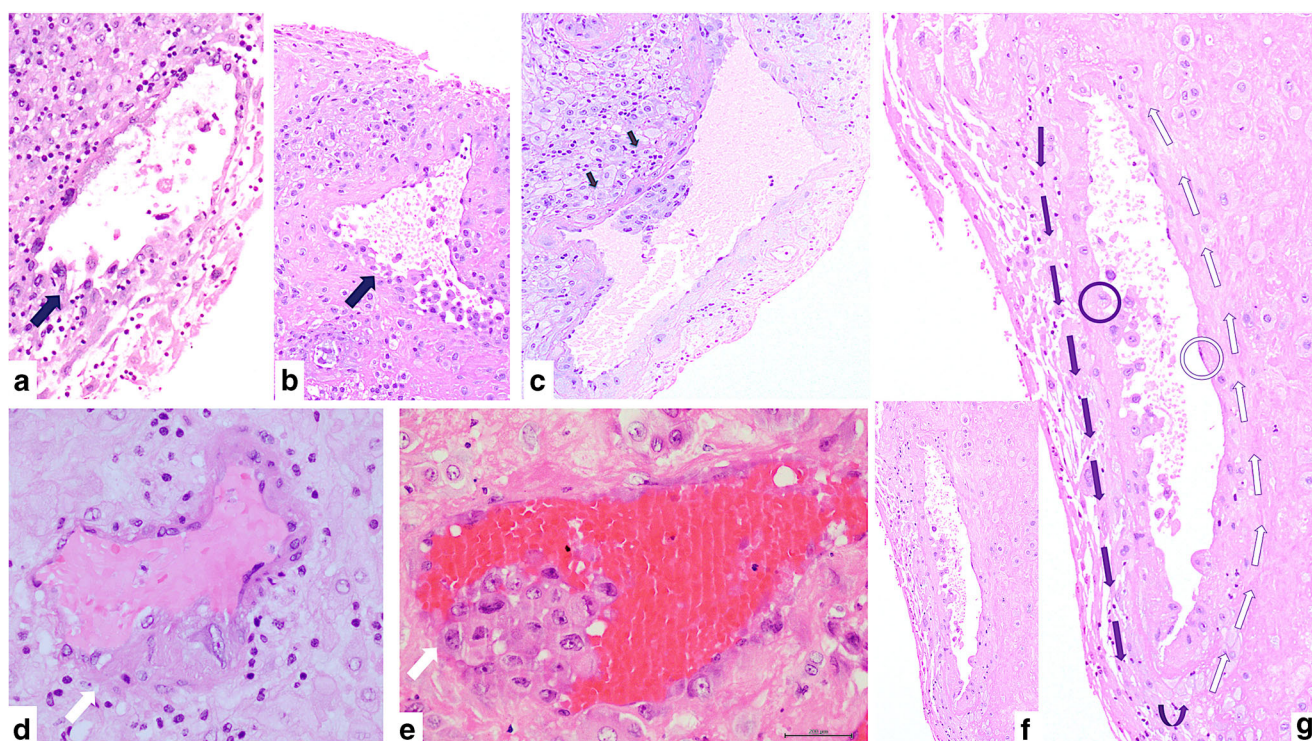
Fig. 2 In each equivalent blood vessel, one edge may show some changes and the other may be in a different phase of the remodeling process. In **a**–**e**, arrows show areas with immature stage compared to contralateral portion of the arterial wall. In **f** and **g**, the same artery exhibits this phenomenon; **g** schematically highlights the asymmetry (black arrows indicate early stage, when trophoblasts line the wall; white arrows, final stage, when endothelium lines the wall) (all H&E photos, decidual portion for spiral arteries)

hyperplastic, is abnormal [29], but it is not possible to determine if it is incomplete, delayed, or deficient. Currently, in early gestations, it is not possible to diagnose abnormal remodeling because of imprecision in relating vessel changes to gestational ages; if research could solve this enigma, we would then be able to classify a number of gestations as having developed clinical preeclampsia.

In our study, we were also unable to explore other unknown relationships, i.e., evidence that artery remodeling is different between first and subsequent gestations [30].

Abnormalities may occur in interior arterial sections of the myometrium and the endometrium [5, 31]; the myometrium portion has been described as being more affected by this pathological condition due to its ultrastructure [32]. However, pathology reports rarely mention myometrial spiral arteries; the standard hypothesis states that decidual artery remodeling is a probable prerequisite for successful myometrial artery remodeling [14]; therefore, decidual anomalies most likely contribute to the formation of myometrial abnormalities.

It worth pointing out that sample collection for decidual arteries is easier in membranes, probably because they are not located in the basal decidua, which are not standard vascular remodeling sampling and evaluation sites. However, it is valid to base abnormal remodeling diagnosis on samples collected from membranes [33]. We based all our study cases on

basal decidua samples. Although research has defined the myometrium portion as the most affected, none of our samples contained myometrial tissue; therefore, it is probable that we failed to identify some abnormal cases in routine samples. Nevertheless, as mentioned, decidual artery remodeling appears to be a prerequisite for correct myometrial artery remodeling. Cases with abnormal decidual remodeling may also have abnormal remodeling of the myometrial artery.

Another limitation in evaluating remodeling is that no descriptions exist on the differences among placental areas; none on gross areas, like center versus edges, nor any on microscopic areas, like nearness to anchoring villous; furthermore, we were unable to determine where the best evaluation site could be. Neither did we know if we were looking at different portions of the same arteries or at many arteries. Nevertheless, we were careful to ascertain whether any case showed deviation for its age, which we could attribute to the number of arteries; however, this scenario showed no impact.

Endovascular trophoblast invasion is not a homogeneous process in the placenta: the density of interstitial extravillous trophoblast and the depth of endovascular extravillous trophoblast invasion of spiral arteries appear predominately in the central region of the basal plate [34], but we did not corroborate this finding in our samples, which came from uterine curettages.
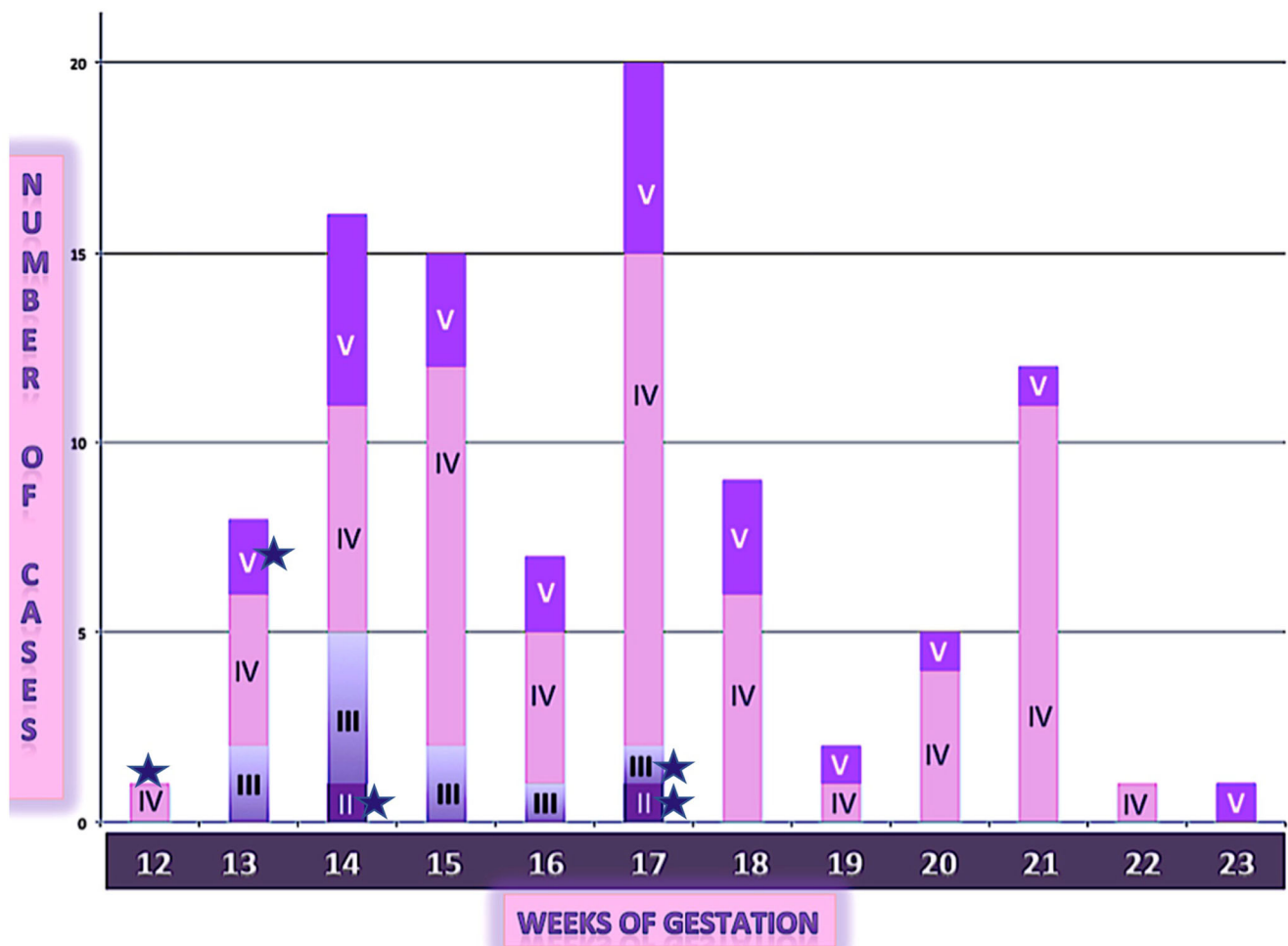
Fig. 3 Weeks of gestation and number of cases in each stage. Stars highlight discordant remodeling results

Stage IV predominated in our population; according to our data, there was no complete remodeling until week 23. This result contradicts that found in the literature, wherein some mention 20 weeks as the end of the remodeling process. The final stage would be stage VI: vein type (not included in either of the two standard classifications).

The novelty of our analysis is the observation on the order in which the changes take place: i.e., the trophoblast seems to receive a signal at the outset of remodeling; this observation suggests that remodeling does not occur randomly; however, we surmise that a link most likely exists between the rotation in the vessel and the asymmetry in the developing left-right axis, the latter being a basic feature of intrauterine development, or that the vessel contains a pole-like identifier where remodeling begins. We have attached a guide (Fig. 3) that displays the expected changes for each gestational age, with the hope of providing a useful tool for identifying abnormal remodeling in miscarriage tissue samples. This guide could also prove useful in counseling families who are deciding on future pregnancies. Our proposal for counseling on planned pregnancies includes a new diagnostic paradigm: "abnormal

remodeling" (abnormal, incomplete, delayed remodeling) which we derived from our study on miscarriage tissue samples. If this data were widely available, physicians could more accurately predict preeclampsia as a possible risk factor for future pregnancies not only in a specific patient, but also in her family.

Controversies on accurately predicting preeclampsia continue to exist, and our study reveals the need for further investigations into the following questions related to normal spiral artery remodeling and its relation to preeclampsia:

1. Is remodeling different in gross areas of the placenta such as the center versus the edges?
2. Is remodeling different microscopically, in areas such as those closer to the anchoring villous, to the subdecidual trophoblast, or to the myometrium?
3. Should we use the term "abnormal remodeling" to describe delayed, partial, absent, or deficient remodeling?
4. Could we relate other gestational changes to the onset of preeclampsia, including persistent trophoblast-lining spiral arteries at term?

5. Could we consider abnormal remodeling as an individual or family-related risk factor for preeclampsia?

6. Could we change the term "mural hypertrophy of maternal arteries" [33] to "mural muscle persistence in maternal arteries," which better describes the process?

7. Could we surmise that a probable relationship exists between the sense of the changes in the same vessel and left-right axis asymmetry?

Although there is currently no consensus on what causes preeclampsia, it is clear that abnormal remodeling in maternal decidua vessels is involved. A better understanding of this disorder requires greater knowledge on the physiological and pathological aspects of the remodeling process. We conclude that muscle and endothelial tissues disappear in the basal decidua arteries from weeks 14 to 17, after which time reendothelialization prevails. According to our study results, at week 23, decidual artery remodeling remains incomplete.

Author Contributions Olaya-C Mercedes: study concept and design, data collection (case search), blinded microscopic review, drafting of manuscript; photography and graphic design, analysis and interpretation of results, final version approval.

Garrido Marta: study concept and design, data collection (case search), drafting of manuscript; final version approval.

Franco, Jorge Andres: study concept and design, blinded microscopic review, drafting of manuscript; final version approval.

Rodriguez, Jorge Luis: blinded microscopic review; final version approval.

Vargas Magda J: blinded microscopic review, drafting of manuscript; photography and graphic design, final version approval.

Aula-Olivar Ana: data collection of (case search), clinical record review, final version approval.

Quintero Laura: graphic design, analysis and interpretation of results, final version approval.

Ramón y Cajal S: study concept and design, data collection (case search); critical review, final version approval.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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