The Burden of Placental Histopathology in Stillbirths Associated With Maternal Obesity

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Key Words: Stillbirth; Obesity; Placenta; Vascular malperfusion; Decidual arteriopathy

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ABSTRACT

Objectives: *Obesity is an increasing health problem that has become a common medical disorder among women of childbearing age, representing worldwide a risk factor for stillbirth. The aim of the study is to evaluate the association between placental histopathologic findings and obesity in stillbirth.*

Methods: *Placentas were analyzed according to the Amsterdam consensus statement. Histologic findings in stillbirth from obese and lean mothers were analyzed and compared with those observed in liveborn controls.*

Results: *Stillbirth in obese mothers displayed placental pathology in all gestational ages, mostly at term of pregnancy. The most observed placental lesions were those consistent with maternal vascular malperfusion of the placental bed. Decidual arteriopathy and placental infarcts appeared specifically associated with maternal obesity. Moreover, obese women with stillbirth showed the highest cumulative number of placental lesions.*

Conclusions: *Considering the significant association between stillbirth, maternal obesity, and placental histopathologic findings, health care providers should be aware about the importance of placental examination in obese women, especially in stillborn cases. The high prevalence of lesions consistent with vascular malperfusion of the placental bed suggests that stillbirth prevention strategies in obese women should rely on the development of tools to study and improve decidual artery functioning early in pregnancy.*

Key Points

- Obesity represents worldwide a risk factor for stillbirth and may affect placental functions.
- Lesions consistent with vascular malperfusion of the placental bed are the most observed in obese women and were significantly associated with stillbirth.
- Histopathologic findings suggest that stillbirth prevention strategies in obese women should rely on the development of tools to study and improve decidual artery functioning early in pregnancy.

Obesity is a pandemic and increasing health problem that has become a common medical disorder among women of childbearing age. In Western countries, maternal obesity affects one-third of women of reproductive age[1] and about one-quarter of pregnant women.[2] Regrettably, according to epidemiologic studies, obesity also represents worldwide an independent risk factor for stillbirth (SB).[3-9] In Italy, despite a lower absolute rate compared with other countries, the prevalence of obesity doubles in women with stillbirth,[10] and the risk of stillbirth increases with increasing maternal weight[11] and with increasing gestational age[8,9]: remarkably, it has been shown that obesity was associated with up to 25% of SBs that occurred between 37 and 42 weeks of gestation.[4]

Previous studies observed that SB in obese women is related to placental pathologies, suggesting that a high body mass index (BMI) may affect placental functions.[12-14] Nowadays, it is generally accepted that placental dysfunctions are one of the main causes of SB.[15] Indeed, the European Association of Perinatal Medicine listed placental histologic examination among the mandatory

actions to promote an adequate investigation and understanding of SB.[16] On the other hand, concerns about the role of placental examination have been previously expressed due to low reproducibility of placental findings determined by different definitions of placental lesions among laboratories.[17,18]

The aforementioned limitations of the placental evaluation have been overcome by the consensus statement recently provided by the Amsterdam Placental Workshop Group,[18] which established uniform, collectively agreed-on terminologies and diagnostic criteria to improve the value of placental histopathologic examination.[18]

The purpose of this study is to apply the Amsterdam criteria to examine the relationship between obesity and the placental lesions associated with SB. The aim is to study the actual burden of placental findings in SBs that occurred in obese women.

Materials and Methods

Study Design and Participants

A retrospective study was carried out on placentas collected from pregnancies that ended in stillbirth or livebirth among lean and obese women.

Eligible cases for the study included singleton pregnancies in which maternal prepregnancy BMI was available. Fetal malformations, abnormal karyotype, and/or intrapartum stillbirth represented criteria of exclusion.

Gestational age was calculated based on the crown-rump length at first-trimester ultrasound.[19] None of the participants was over 42 weeks of gestation.

Pregestational BMI was calculated according to the standard formula (kg/m^2). Patients were considered obese with a pregestational BMI of 30.0 kg/m^2 or more.[20]

SB was defined as intrauterine fetal death occurring from 22 weeks of gestation, according to the World Health Organization's International Statistical Classification of Diseases, 10th revision.[21]

Cases included 36 placentas from pregnancies that ended in antepartum SB in obese women, 14 of them occurring at term (≥37 weeks of gestation). These latter cases (named SB-obese) were compared with three groups of controls (ratio 1:2), matched for gestational age (same week of gestation ± 6 days):

- SB in women with normal BMI (n = 28; named SB-lean)
- Uneventful singleton pregnancies in obese women (n = 28, named livebirth [LB]-obese)
- Uneventful singleton pregnancies in women with normal BMI (n = 28, named LB-lean)

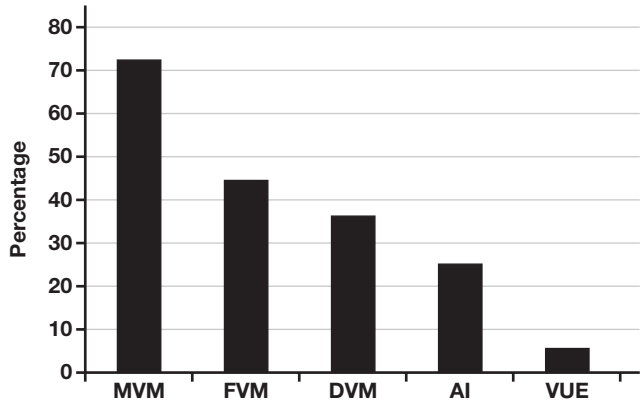

Figure 1 "Placentosity": placental lesions affecting stillbirth associated with maternal obesity. Prevalence of placental lesions observed in stillborn cases from obese women (prepregnancy body mass index ≥30.0 kg/m^2), from 22 to 42 weeks of gestation (n = 36). The high prevalence of placenta lesions associated with obesity suggests the neologism "placentosity" (placenta and obesity). For each category, percentages of cases in which at least one lesion was present are shown. MVM was the most observed category of placental lesions (26/36 cases showed at least one MVM lesion). FVM was the second most observed category (16/36 cases showed at least one FVM lesion). Delayed villous maturation was the third observed category (13/36 cases). AI and VUE affected a minority of cases, occurring respectively in nine of 36 and two of 36 cases. AI, ascending infection; DVM, delayed villous maturation; FVM, fetal vascular malperfusion; MVM, maternal vascular malperfusion; VUE, villitis of unknown etiology.

Those 84 control placentas were randomly selected among women who delivered during the same time period. Placentas from uneventful pregnancies were obtained from a data set of placental analyses established for research purposes.

The study flowchart is summarized in Supplementary Figure 1 (all supplemental materials can be found at *American Journal of Clinical Pathology* online).

Ethical Issues

Ethical approval was obtained from the local institutional review board (0024036/2018; date of approval September 26, 2018). The methodology is in accord with the Declaration of Helsinki.

The study was retrospective, and therefore patients' signed release forms were unobtainable. On the other hand, the study was performed in university hospitals, and the data in question were obtained with the patients' understanding that they might be published.

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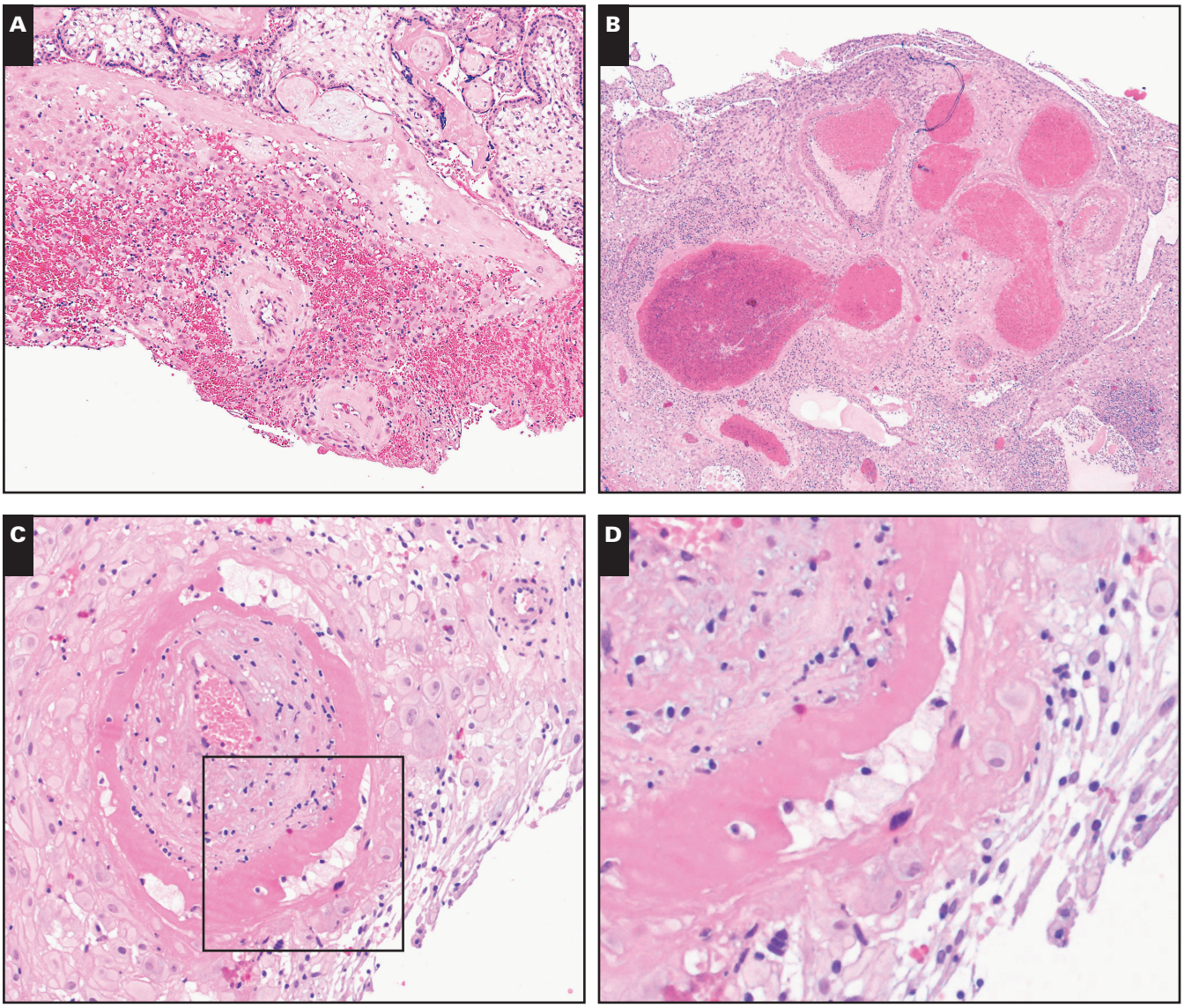

Image 1 Histologic features of the most observed placental lesions in stillborn cases from obese women, from 22 to 42 weeks of gestation (n = 36) (H&E). **A-H**, Lesions consistent with maternal vascular malperfusion (MVM) of the placental bed. Decidual arteriopathy was the most observed feature among MVM: 18 of 36 cases displayed absence or incompleteness of spiral artery modeling with retention of musculoelastic elements in the arterial wall (**A**; 13 cases) and/or arterial thrombosis (**B**; six cases) and/or acute atherosis (**C**, **D**; five cases; **D** shows framed area in **C**).

Placental Evaluation

Placentas were analyzed by an expert perinatal pathologist (G.P.B.) following the standard protocol proposed by the Amsterdam consensus statement.[18] The pathologist was blinded to clinical characteristics but gestational age, since some of the pathologic findings were closely dependent on gestational age (ie, maturation of placental parenchyma). Other clinical parameters were not provided to the pathologist until the end of histologic review.

At least five slides stained with H&E were analyzed for each case: one slide containing a roll of free membranes from the ruptured edge to the placental margin, one slide containing three cross sections of umbilical cord, and three slides each containing a full-thickness section of normal-appearing placental parenchyma. If macroscopic placental lesions were noted, additional slides containing representative specimens with adjacent normal parenchyma were also analyzed.

Placental lesions were diagnosed and classified according to the Consensus Statement of the Amsterdam Placental Workshop Group.[18] The categories of lesions include maternal vascular malperfusion (MVM) of the placental bed, fetal vascular malperfusion (FVM),

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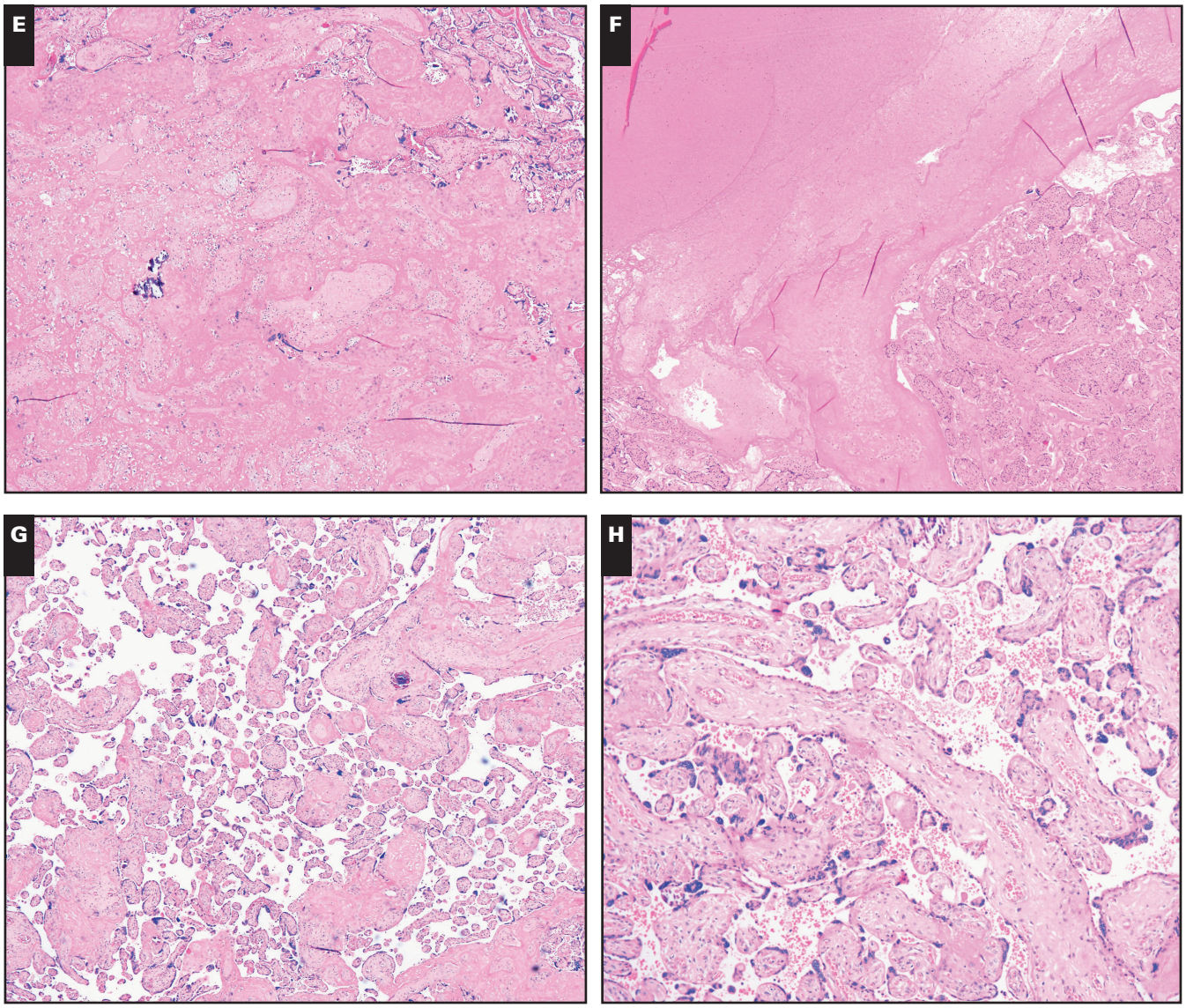

Image 1 (cont) Consequences of decidual arteriopathies included placental infarcts (**E**; 11/36 cases) or retroplacental hemorrhage (**F**; 6/36 cases). Malperfusion of the placental bed may interfere with villi development, leading to distal villous hypoplasia (**G**; 2/36 cases) and accelerated villous maturation (**H**; 7/36 cases).

delayed villous maturation, ascending intrauterine infection, and villitis of unknown etiology. To ensure the discrimination between ante- and postmortem histopathology findings, we applied the considerations provided by Boyd[22] in 2018.

Statistical Analyses

The placental characteristics were compared between patients with/without obesity and with/without stillbirth, using the χ^2 test or Fisher exact test, as appropriate, for categorical variables. $P < .05$ was considered statistically significant. For the significant placental lesions, odds ratios with respective 95% confidence intervals were further estimated to assess the burden of placental disease.

Results

Placental Lesions Throughout Gestation in Obese Women With SB

All categories of placental lesions were present in obese women with SB. Their prevalence is reported in Figure 1, and representative images of the most prevalent lesions are shown in Image 1.

MVM of the placental bed was the most common category, affecting 26 (72.2%) of 36 cases. Among them, 12 (46.1%)

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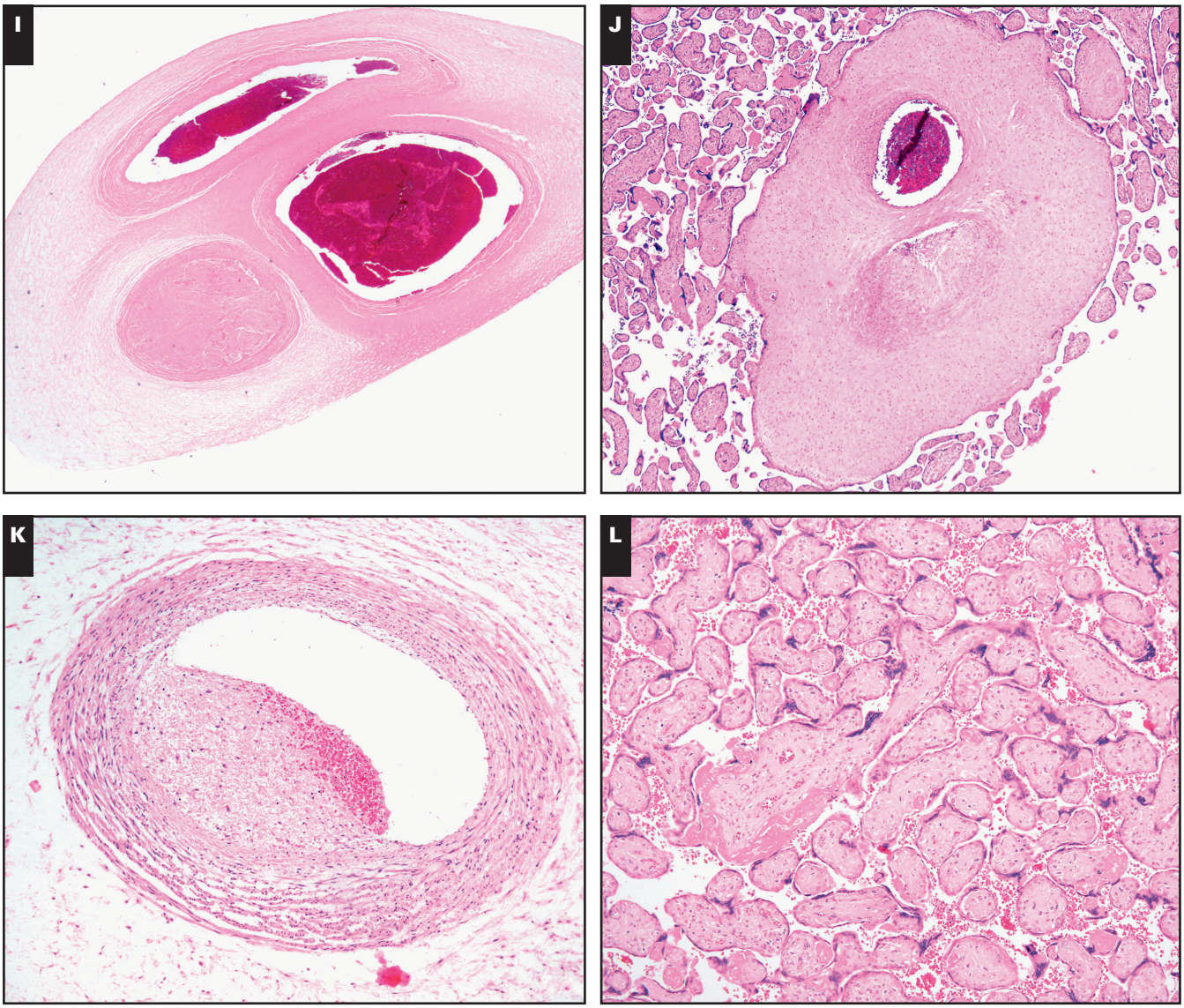

Image 1 (cont) **I-L**, Lesions consistent with fetal vascular malperfusion. Thrombosis of umbilical cord (**I**; 11/36 cases), stem vessel obliteration (**J**; 8/36 cases), intramural fibrin deposition (**K**; 5/36 cases), and avascular villi (**L**; 11/36 cases).

of 26 cases showed more than one lesion consistent with MVM. Placentas with MVM also presented at least one lesion consistent with decidual arteriopathy in 18 (69.2%) of 26 cases. These included absence of spiral artery remodeling (13/18 cases; Image 1A), arterial thrombosis (6/18 cases; Image 1B), and acute atherosis (5/18 cases, Images 1C and 1D).

FVM was the second most common category observed, occurring in 44.4% of cases (16/36 cases; 11/16 cases were affected by more than one lesion) while delayed villous maturation affected 36.1% of cases (13/36 cases).

Villitis of unknown etiology affected a minority of cases (2/36 cases; 5.5%) as well as ascending infection (9/36 cases showed signs of maternal inflammatory response, but only three presented signs of fetal inflammatory response, accounting for 8.3% of cases).

The simultaneous presence of different categories of lesions occurred in 66.7% of cases (24/36 cases), especially with regard to MVM and FVM, which were both present in 11 of 24 cases. Details about coexisting categories of placental abnormalities are reported in Supplementary Table 1.

The distribution of placental lesions according to gestational age is reported in Supplementary Figure 2. Term pregnancies showed the highest prevalence of lesions.

Placental Lesions at Term of Pregnancy

Comparative details of maternal clinicodemographic characteristics are shown in **Table 1**. This is an important issue to warrant that the prevalence of placental lesions was not biased by confounders factors: in our population,

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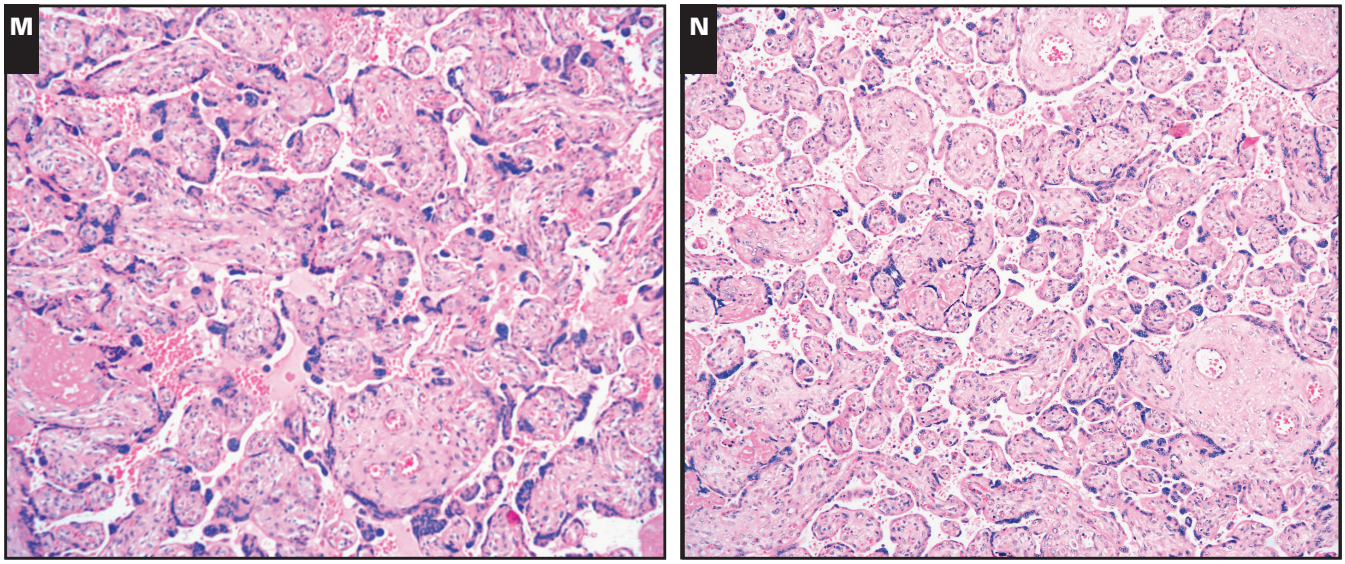

Image 1 (cont) **M**, **N**, Lesions consistent with delayed villous maturation. Monotonous villous population with centrally placed capillaries and decreased vasculosyncitial membranes (**M**, **N**; 9/36 cases).

Table 1
Demographic Characteristics in Cases and Controls in Term Pregnancies[a]

Category	SB-Obese (n = 14)	SB-Lean (n = 28)	LB-Obese (n = 28)	LB-Lean (n = 28)
Prepregnancy BMI, median (range), kg/m^2	32.2 (30.1-53.1)	22 (18.6-24.8)	33.2 (30.1-42)	22.9 (19.4-24.9)
Maternal age, median (range), y	33 (20-40)	33(19-40)	29 (18-37)	33.5 (24-42)
Prepregnancy hypertension	1 (7.1)	0	0	0
Preeclampsia	0	0	0	0
IDDM	2 (14.3)	0	0	0
GDM	1 (7.1)	1 (3.6)	0	0
Male newborn	10 (71.4)	14 (50)	16 (57.1)	15 (53.6)
Neonatal weight, median (range), g	2,600 (2,266-4,895)[b]	3,038 (2,330-4,180)	3,465 (2,550-3,970)	3,170 (2,440-3,970)
Birth weight <10th percentile	5 (35.7)[c]	6 (21.4)	0	2 (7.1)
High grade of fetal maceration	0	0	0	0

BMI, body mass index; GDM, gestational diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; LB, livebirth; SB, stillbirth.
[a]Data are expressed as number (%) unless otherwise indicated. All stillbirths included recent/fresh fetal death. This could be related to the maternal awareness of fetal moving at term of pregnancy, leading to a short timeframe between the fetal death and the diagnosis and between the death, labor, and delivery. None of cases were diagnosed as "fetal growth restriction" during pregnancy. Cases with unexpected birth weight less than the 10th percentile were identified after delivery. The prevalence of birth weight less than the 10th percentile in SB could be related to the high prevalence of placental lesions; therefore, it could be a clinical consequence of the maternal vascular malperfusion and not a confounder factor.
[b]$P < .05$ compared with all other categories.
[c]$P < .05$ compared with LB categories.

chronic hypertension, diabetes, and preeclampsia were comparable among groups, and fetal maceration was absent. Therefore, the results are unlikely to have been affected by these potential confounding factors.

Table 2 reports placental lesions at term of pregnancy in cases compared with controls.

In SB, obese mothers showed a higher prevalence of placental infarcts compared with lean mothers (SB-obese 42.8% vs SB-lean 14.3%, $P < .05$), as well as a higher prevalence of decidual arteriopathy (SB-obese 42.8% vs SB-lean 21.4%, $P < .05$). Cumulative prevalence of lesions consistent with decidual arteriopathy in SB-obese and SB-lean is shown in Figure 2, and images are shown in Image 2.

Comparing placental findings in SB-obese and LB, the prevalence of many lesions consistent with MVM (placental infarcts, decidual arteriopathy) and with FVM (thrombosis and obliteration of fetal vessels with intramural fibrin deposition and avascular villi) was significantly higher in SB-obese than in LB (Table 2 and Figure 3).

Lesions consistent with delayed villous maturation or fetal inflammatory response or villitis of unknown etiology did not differ between groups (Table 2).

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Table 2
Placental Lesions in Cases and Controls in Term Pregnancies[a]

Category	SB-Obese (n = 14)	SB-Lean (n = 28)	LB-Obese (n = 28)	LB-Lean (n = 28)
Maternal vascular malperfusion				
Infarcts	**6 (42.8)[b]**	4 (14.3)	0	3 (10.7)
Hemorrhage	1 (7.1)	5 (17.8)[c]	0	0
Distal villous hypoplasia	1 (7.1)	0	0	0
Accelerated villous maturation	1 (7.1)	6 (21.4)	5 (17.8)	5 (17.8)
Decidual arteriopathy	**6 (42.8)[b]**	6 (21.4)	4 (14.3)	2 (7.1)
Fetal vascular malperfusion				
Thrombosis	**6 (42.8)[c]**	12 (42.8)[c]	1(3.6)	0
Avascular villi	**4 (28.5)[c]**	7 (25.0)	1 (3.6)	1 (3.6)
Intramural fibrin deposition	**4 (28.5)[c]**	8 (28.5)[c]	0	0
Villous karyorrhexis	1 (7.1)	1 (3.6)	0	0
Stem vessel obliteration	**3 (21.4)[c]**	5 (17.8)	0	0
Vascular ectasia	1 (7.1)	1 (3.6)	0	0
Delayed villous maturation	7 (50.0)	9 (32.1)	5 (17.8)	5 (17.8)
Acute inflammation				
Maternal inflammatory response	5 (35.7)	10 (35.7)	3 (10.7)	0
Fetal inflammatory response	3 (21.4)	3 (10.7)	0	0
Villitis of unknown etiology	1 (7.1)	7 (25)	2 (7.1)	5 (17.8)
No. of cumulative lesions	50	78	21	21

LB, livebirth; SB, stillbirth.
[a]Data are expressed as numbers (%). Numbers in bold are statistically significant.
[b]$P < .05$ compared with all other categories.
[c]$P < .05$ compared with LB categories.

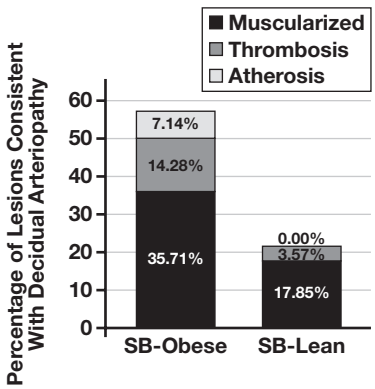

Figure 2 Prevalence of lesions consistent with decidual arteriopathy in SB-obese and SB-lean. In SB-obese, five of 14 cases presented with incomplete or absent arterial modifications, showing retention of musculoelastic elements in the arterial wall, two of 14 cases showed arterial thrombosis, and one of 14 cases showed acute atherosis. In SB-lean, five of 28 cases showed retention of musculoelastic elements in the spiral arterial wall, one of 28 cases showed arterial thrombosis, and none of the cases had acute atherosis. Cumulative odds ratio = 4.88 (95% confidence interval, 1.2-19.6); $P = .025$. SB, stillbirth.

Multiple placental lesions affected more frequently SB-obese (50 lesions/14 cases) than SB-lean (78 lesions/28 cases) and LB (21 lesions/28 cases, both in LB-obese and LB-lean) with an estimated average of lesions per case of 3.6 in SB-obese, 2.8 in SB-lean, and 0.75 in LB.

Discussion

Stillbirth represents a dramatic and devastating event for parents, especially when it takes place late in pregnancy. Many risk factors have been recognized both worldwide and in Italian cohorts,[10,13,23,24] including maternal obesity and placental pathologies. The present study focused attention on both these aspects: placental pathologies in stillbirths occurred in obese pregnant women.

Strengths and Limits

The main strength of the present study is the application of a systematic and rigorous approach to classify placental pathologies to emphasize the real contribution of placental findings. This approach avoids the limits related to inconsistent coding and definitions.

Another strength is represented by the blinded placental examination performed by the pathologist, thereby avoiding bias.

We also acknowledge the limitations of our study: the retrospective design limited the availability of maternal anthropometric data, reducing the sample size. Nevertheless, the strong correlation that we found between placental pathologic findings and pregnancy outcome is notable, although 95% confidence intervals were large.

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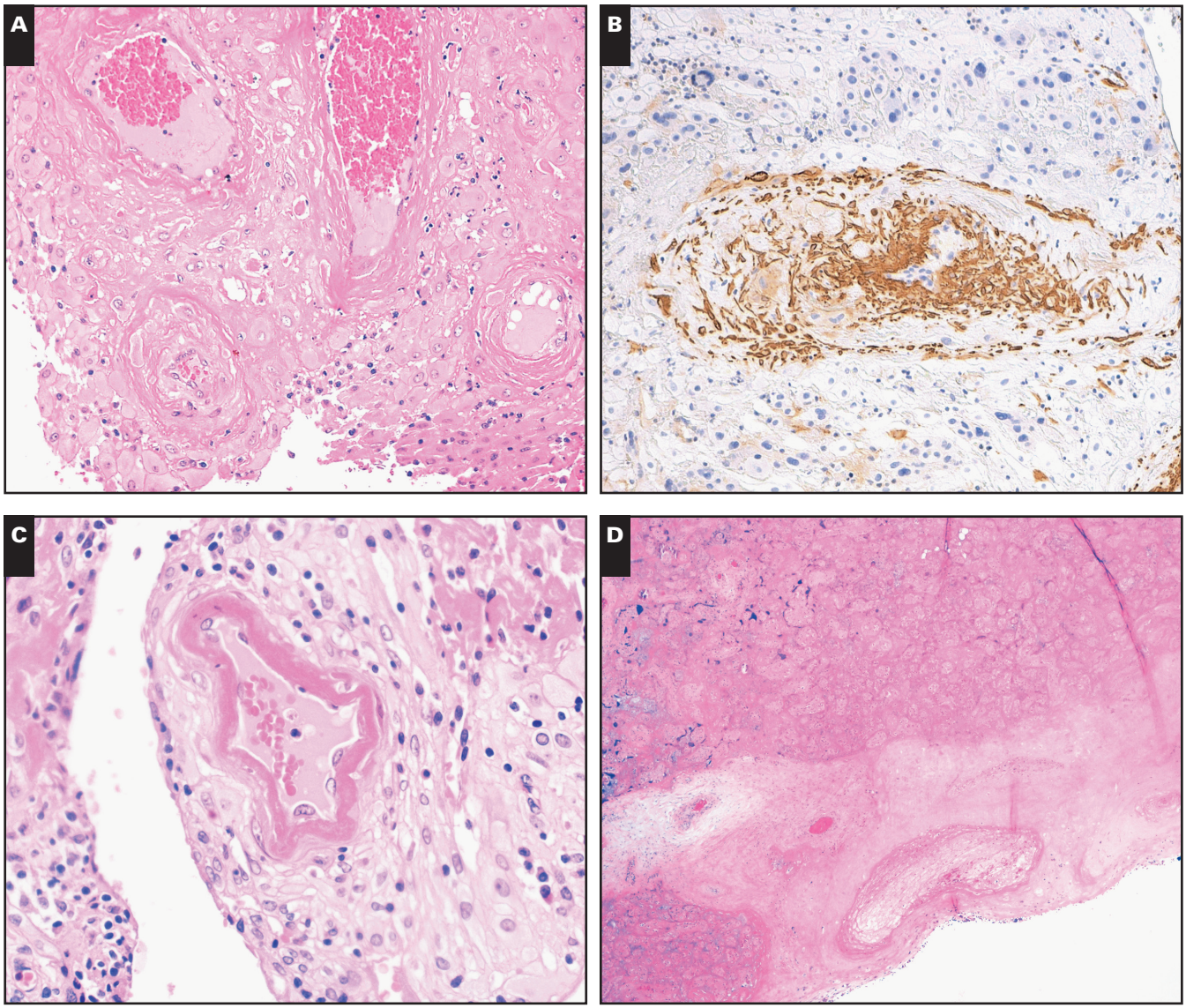

Image 2 Lesions consistent with decidual arteriopathy. **A**, Abnormal modeling of maternal artery with retention of musculoelastic arterial wall (H&E, ×40). **B**, To confirm and emphasize the feature of the abnormality of arterial remodeling, immunohistochemical reaction with α–smooth muscle actin antibody demonstrates the presence of smooth muscle in the wall of a maternal spiral artery (×40). **C**, Fibrinoid necrosis of small maternal spiral artery with lipid-laden macrophages in the wall (acute atherosis) (H&E, ×40). **D**, Infarction of the placenta due to the underlying maternal spiral artery thrombosis (H&E, ×20).

Main Findings

The most common placental lesions we observed were those consistent with malperfusion on the maternal and fetal vascular side of the placenta. In women at term of pregnancy, such lesions were significantly higher in stillborn cases affecting obese women compared with liveborn controls. Decidual arteriopathy and placental infarcts appeared specifically associated with maternal obesity, being more frequent in obese than in lean mothers affected by SB. The other categories of placental lesions did not appear to be associated with obesity in stillbirth in our population. The possible association between maternal obesity and placental inflammation is a debated issue.[25,26] It was especially associated with female fetal sex[25]; therefore, the lack of association between maternal obesity and placental inflammation in our stillborn cases may be related to the high prevalence of male fetuses.

Interestingly, major placental pathology was not found in the LB-obese group compared with the SB-obese group, suggesting that other factors may be needed to trigger the effect of obesity on placental maldevelopment. Our population was comparable for maternal demographic data;

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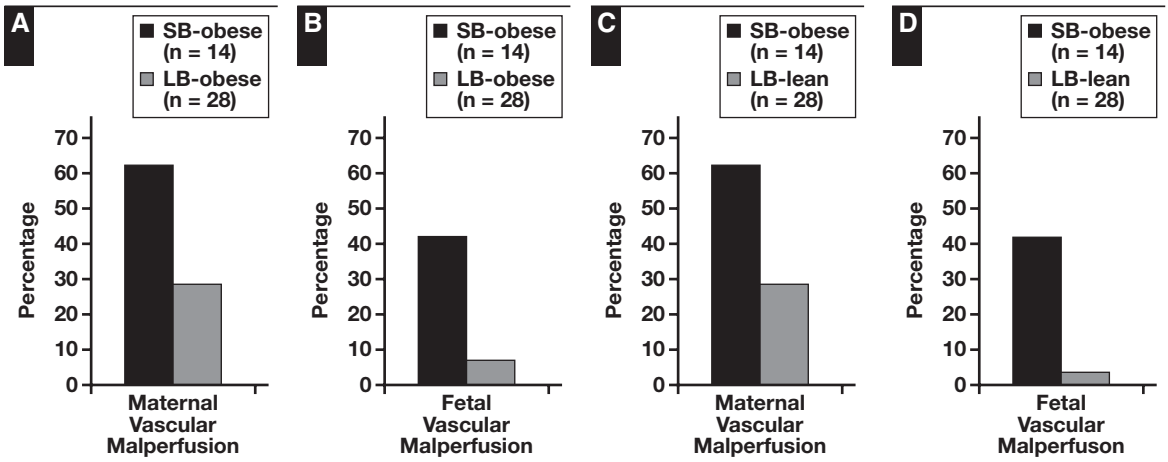

Figure 3 Vascular placental lesions in SB-obese vs LB-obese (**A**, **B**) and LB-lean (**C**, **D**). Percentages include cases in which at least one lesion was present. Lesions consistent with maternal vascular malperfusion and fetal vascular malperfusion were higher in SB-obese than LB, with a significant odds ratio (OR). **A**, OR = 4.5 (95% confidence interval [CI], 1.1-17.6), $P = .04$. **B**, OR = 9.7 (95% CI, 1.6-58.1), $P = .01$. **C**, OR = 1.15 (95% CI, 1.1-17.6), $P = .04$. **D**, OR = 20.2 (95% CI, 2.1-193.9), $P = .003$. LB, livebirth; SB, stillbirth.

therefore, further studies need to identify players within the portfolio of obesity-associated factors able to affect the intrauterine environment and to lead critical consequences for placental development and fetal well-being.

MVM and Adverse Pregnancy Outcome

As observed in the present study, histologic features of MVM include placental infarcts, retroplacental hemorrhage, abnormal placental villous maturation, and decidual arteriopathy.[18] It is well known that MVM due to decidual arteriopathy leads to the so-called defective deep placentation, leading in turn to major obstetrical syndromes[27] and stillbirth.[28] Adverse pregnancy outcomes may be related to incomplete or absent remodeling of arterial muscular walls of the spiral arteries: this may reduce blood flow and/or give rise to high-speed blood flow rates, resulting in chorionic villi damage, hypoxia/reperfusion injury, and oxidative stress.[29] Obese women have been found to show these placental damages and to be at higher risk of MVM[11,30] and MVM-related stillbirth.[31] The present study confirms and highlights the association between stillbirth and MVM, especially in obese women with decidual arteriopathy.

The clinical challenge is to overcome the major limit posed by the identification of such relevant features only when the placenta becomes available for histologic examination, that is, after the third stage of labor. Ideally, signs of MVM should be detected before placental expulsion and before the occurrence of clinical symptoms and adverse pregnancy outcomes. Ultrasound examinations of the placenta together with uterine artery Doppler evaluation are promising tools in detecting signs of placental maldevelopment and dysfunction. Kim et al[32] showed that women with high BMI had signs of vascular impedance in uterine arteries more than twice as high compared with women with a normal BMI. This is an important finding, and it may be useful in predicting the occurrence of adverse obstetrical outcomes related to MVM in obese women.[32]

FVM and Adverse Pregnancy Outcome

Maternal BMI may also affect umbilical artery Doppler velocimetry.[33] Abnormal umbilical artery Doppler velocimetry reflects an increase in fetoplacental vascular impedance. Histologic lesions consistent with fetal vascular malperfusion may be found in many sites along the vascular tree, starting from umbilical vessels through chorionic vessels and stem villi, ending with the terminal villi,[34] with temporal and spatial heterogeneity to the pattern, warranting its occurrence before the fetal demise.[22] Accordingly, this was documented in our cases, with FVM the second most common finding in SB cases. However, the prevalence of FVM was comparable in SB from obese and lean mothers, losing specificity with regard to maternal BMI.

Cumulative Placental Lesions

Even though MVM and FVM can each be separated into distinct patterns,[35] many features are frequently

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interrelated,[35] and it is common to find more than one lesion in placental pathology. The number and magnitude of relevant findings may worsen placental functions with potential clinical relevance,[35] as occurred in our population. Indeed, stillbirths in obese women showed the highest cumulative number of placental lesions.

Summary

In summary, our data suggest that the well-known high risk of adverse outcome among obese mothers[36] may be associated with placental pathologies. Our findings highlight that placental histology displays abnormal features throughout the whole gestation in obese mothers with SB, and such pathologic findings become significantly remarkable toward the end of gestation. The most common placental abnormality at term is consistent with vascular malperfusion of the placental bed. Hence, health care providers should be aware about the importance of placental examination in obese women, especially in stillborn cases; stillbirth prevention strategies in obese women should address the role of decidual arteriopathy. Tools for its early evaluation need to be developed in the future.

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