# Placentas From Women of Advanced Maternal Age

## An Independent Indication for Pathologic Examination?

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• ***Context.***—**The percentage of pregnant women with advanced maternal age (AMA) has increased during the past several decades due to various socioeconomic factors and advances in assisted reproduction. These pregnancies are associated with adverse maternal and fetal outcomes. However, the underlying placental pathology has not been well described.**

***Objective.***—**To investigate the placental histopathology associated with AMA pregnancies.**

***Design.***—**Placental pathology from 168 AMA women 35 years or older at delivery was reviewed. The cases were subdivided into 2 age subgroups, ages 35 to 39 and 40 or older, as well as a "pure AMA" subgroup where the only indication for placental examination was AMA. A group of 60 consecutive non-AMA placentas was also identified and used as comparison. The spectrum of histologic features in each case was catalogued.**

***Results.***—**Of the overall AMA cases, meconium deposition was seen in 55% (93 of 168), chorangiosis in 40% (68 of 168), and acute chorioamnionitis in 36% (60 of 168). Fetal vascular malperfusion was also seen with high frequency (30%; 50 of 168). Two histologic alterations found to be significantly different between the 35 to 39 and greater than 40 age subgroups were fetal vascular malperfusion (11% [7 of 65] versus 42% [43 of 103]; $P = .001$) and delayed villous maturation (1.5% [1 of 65] versus 13% [13 of 103]; $P = .02$). The pure AMA subgroup showed no statistically significant differences compared with the overall AMA group. Chronic deciduitis was the only statistically significant difference between the overall AMA group and the non-AMA comparison group (14% [23 of 168] versus 30% [18 of 60]; $P = .02$).**

***Conclusions.***—**Our findings, particularly the high frequency of fetal vascular malperfusion, suggest that AMA should be an independent indication for placental pathologic examination.**

**(*Arch Pathol Lab Med.* 2020;144:1254–1261; doi: 10.5858/arpa.2019-0481-OA)**

Pregnancies classified as complicated with advanced maternal age (AMA) are defined when the maternal age is greater or equal to 35 years at the estimated date of delivery.[1,2] Because of various socioeconomic factors, including delayed age at marriage, pursuit of advanced education and careers, and higher rates of divorce and remarriage, as well as the development of, and advancements in, assisted reproductive technologies, the prevalence of pregnancies associated with AMA has been increasing.[3–10] In the United States, the mean maternal age at the time of birth has risen to 28.8 years; for comparison, in 1998 it was 24.3 years and in 1972 was 22.0 years.[11,12]

There is a large body of literature that has investigated the impact of AMA on maternal and fetal outcomes. Although reports have varied,[1,13–15] AMA has been associated with adverse maternal and fetal outcomes and pregnancy complications, including increased risk for gestational diabetes, preeclampsia, placenta previa, macrosomia, preterm birth, stillbirth, and increased rates of cesarean delivery; very AMA (vAMA; age >40 or 45 at the time of delivery, depending on the study) has also been associated with higher risks of low birth weight, stillbirth, and perinatal death.[6,7,10,16–32] Despite the expansive literature investigating maternal and fetal outcomes associated with AMA, the pathogenic mechanisms underlying the increased associated risks remain largely unknown. This is complicated further by the increased use of fertility treatments and oocyte donation, which in and of themselves have also been associated with a number of increased risks, including preeclampsia and prematurity,[33,34] and other potential factors, such as higher parity and higher probability of having had previous uterine procedures.

While studies have investigated the impact of AMA on pregnancy outcomes, there is a lack of literature regarding the histologic findings in these placentas. Although AMA has been shown to be associated with placenta accreta and placenta previa,[35–38] to date few studies have specifically and comprehensively detailed the histopathologic findings in the placentas from these women. At our institution, it is our current practice to evaluate all placentas from women of age 40 years and older, even if this is the sole indication for

Accepted for publication January 8, 2020.
Published online February 26, 2020.

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The authors have no relevant financial interest in the products or companies described in this article.

Presented at the 108th United States and Canadian Academy of Pathology Annual Meeting; March 20, 2019; National Harbor, Maryland.

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examination. The aim of this study was to perform an in-depth assessment of the histopathologic findings in the placentas of AMA women to investigate if there are any underlying pathologic alterations in the placentas from these women that may account for, or correlate with, the reported increased perinatal morbidity.

## MATERIALS AND METHODS

We retrospectively searched the archives of the Massachusetts General Hospital Department of Pathology during the time period of August 2008 to March 2019 for all placenta specimens where the provided clinical history included "advanced maternal age." For all cases, all of the provided clinical history/indications for pathologic examination were documented (which may not have been solely AMA).

The placenta weight and other pertinent information from the gross description, including umbilical cord insertion, umbilical cord coiling, and membrane insertion, were documented. Of note, the following definitions are used at our institution: hypocoiling is 1 or fewer coils per 10 cm of umbilical cord and hypercoiling is 4 or more coils per 10 cm; peripheral umbilical cord insertion is insertion 2 cm or less from the disc margin and marginal insertion is 1 cm or less from the disc margin; any degree of circummargination or circumvallation was noted. Placental weight for gestational age was derived using set reference values.[39]

All hematoxylin and eosin–stained slides for each case were rereviewed by a pathologist with subspecialty training in obstetrical pathology (VFT). A variety of histologic alterations were catalogued, as outlined in Table 1 (with accompanying definitions as relevant). Briefly stated here, each case was assessed for histologic chorioamnionitis, which was graded and staged according to the structure proposed by the Society for Pediatric Pathology[40] and reaffirmed by the Amsterdam placental workshop group consensus statement on sampling and defining placental lesions.[41] Villitis of unknown etiology was graded following the Amsterdam guidelines.[41] Fetal vascular malperfusion (FVM) and maternal vascular malperfusion were also defined and graded according to the Amsterdam guidelines.[41] Chronic deciduitis was diagnosed if there was at least one high-power field with greater than 50 lymphocytes identified, and was further qualified as plasma cell deciduitis if 5 or more plasma cells were seen in any one high-power focus.[42,43] Another alteration evaluated was delayed villous maturation, which morphologically is characterized by increased distal villous size with increased stromal cellularity and extracellular matrix, increased cytotrophoblast cellularity, and centrally placed capillaries with reduced vasculosyncytial membrane formation. At least 30% of one full-thickness slide had to have been involved for delayed villous maturation to have been diagnosed (with gestational age taken under consideration).[41]

In efforts to evaluate any differences between AMA and vAMA, the data were further evaluated by subdividing the AMA group into cases where the mother was age 35 to 39 and those of women greater than or equal to age 40. As noted previously, the placentas in this cohort were selected for the study if the clinical indication was AMA even if it was not the sole indication. Thus, an additional subgroup was of the "pure" AMA mothers (ie, those placentas where the sole clinical indication for pathologic examination was AMA; the electronic medical record was searched in these cases to confirm there were no other indications aside for AMA). Given the fact that the majority of our AMA cases have confounders (>1 clinical indication for pathologic examination, ie, aside from AMA), we evaluated an additional comparison group of 60 consecutive all-comer placentas from women less than 35 years of age (which had at least one clinical indication for examination). "Normal" placentas (those without clinical indication) are not examined at our institution.

The frequency of histologic features in each of the study groups was compared using $X^2$ and Fisher exact tests, as appropriate. Two-sided $P$ values of $<.05$ were considered statistically significant. The study received institutional review board approval by the Massachusetts General Hospital Committee for Clinical Investigations.

**Table 1. Histologic Features Evaluated**

| Meconium Deposition |
|---|
| Maternal inflammatory response |
| Stage 1 – Acute subchorionitis or chorionitis |
| Stage 2 – Acute chorioamnionitis |
| Stage 3 – Necrotizing chorioamnionitis |
| Fetal inflammatory response |
| Stage 1 – Chorionic vasculitis or umbilical phlebitis |
| Stage 2 – Involvement of umbilical vein and one or more umbilical arteries |
| Stage 3 – Necrotizing funisitis |
| Villitis of unknown etiology |
| Low Grade – Inflammation involving <10 contiguous villi in any one focus; >1 focus needed |
| High Grade – Inflammation involving >10 contiguous villi; more than one focus needed; >1 section |
| Fetal vascular malperfusion |
| Low Grade – One occlusive or nonocclusive thrombus and/or scattered avascular villi (<45 cumulative or average <15 per section) |
| High Grade – Two or more occlusive or nonocclusive thrombi, multiple nonocclusive thrombi, and/or significant avascular villi |
| Maternal vascular malperfusion |
| Need at least 2 features from the following: placental weight <10th percentile for gestational age, >2 marginal or any central infarct, thin umbilical cord, any feature of abruption, or decidual arteriopathy |
| Grade 1 (mild to moderate) – normal placental weight, <30% involvement by pathology, no more than one marginal infarct |
| Grade 2 (severe) – placental weights <10th percentile, >30% of the parenchyma involved with pathology, multiple nonmarginal infarcts |
| Placental infarct – All-comers, either as part of maternal vascular malperfusion or if found as a finding without other features fitting the umbrella term of maternal vascular malperfusion |
| Intervillous thrombus |
| Chorangiosis – More than 10 capillaries per terminal villous, in 10 villi, in >10 areas/fields |
| Delayed villous maturation – At least 10 villi with centrally placed capillaries and decreased vasculosyncytial membranes present in at least 30% of one full-thickness slide |
| Villous edema |
| Chronic deciduitis – Greater than or equal to 50 lymphocytes per high-power field (includes cases further specified as plasma cell deciduitis per definition below) |
| Plasma cell deciduitis – Greater than or equal to 5 plasma cells per high-power field |
| Decidual arteriopathy |
| Basal plate myometrial fibers |

## RESULTS

A total of 168 placentas with a clinical indication, including AMA, were identified. The clinical and gross findings of the overall AMA cases and the two age subgroups are shown in Table 2. Overall, the average age of the mothers at the time of delivery was 40.1 years and the median age was 40 years. The age range was 35- to 51-years old. The average gravidity was 3.2 and the parity was 2.2.

**Table 2. Clinical and Gross Findings of Overall Advanced Maternal Age (AMA) Cases, AMA Age Subgroups, and Non-AMA Comparison Group**

| | Overall AMA, N = 168 | Age 35–39 (rAMA), N = 65 | Age >40 (vAMA), N = 103 | Non-AMA Comparison Group, N = 60 |
|---|---|---|---|---|
| Age, y | | | | |
| Average | 40.1 | 37.1 | 41.9 | 30.1 |
| Median | 40 | 37 | 41 | 31 |
| Ethnicity | | | | |
| African American | 15 (8.9%) | 7 (10.8%) | 8 (7.7%) | 2 (3.3%) |
| Asian | 10 (6.0%) | 3 (4.6%) | 7 (6.8%) | 7 (11.7%) |
| Hispanic | 17 (10.1%) | 6 (9.2%) | 11 (10.7%) | 14 (23.3%) |
| White | 126 (75.0%) | 49 (75.4%) | 77 (74.8%) | 37 (61.7%) |
| Body mass index (gravid) | | | | |
| Average | 28.0 | 27.4 | 28.2 | 28.4 |
| Median | 27.0 | 26.5 | 27.4 | 27.5 |
| Gravidity (average) | 3.2 | 2.8 | 3.4 | 3.6 |
| Parity (average, postpartum) | 2.2 | 2.2 | 2.3 | 2.5 |
| Weeks gestational age at time of delivery | | | | |
| Average | 38.6 | 38.4 | 38.7 | 39.1 |
| Median | 39 | 39 | 39 | 39 |
| Other clinical indications | | | | |
| Maternal diabetes | 20 (11.9%) | 6 (9.2%) | 14 (13.6%) | 2 (3.3%) |
| Hypertension/preeclampsia | 16 (9.5%) | 7 (10.8%) | 9 (8.7%) | 8 (13.3%) |
| GBS positive | 16 (9.5%) | 6 (9.2%) | 10 (9.7%) | 0 (0%) |
| Anemia/thrombocytopenia | 15 (8.9%) | 6 (9.2%) | 9 (8.7%) | 0 (0%) |
| Other maternal disease | 15 (8.9%) | 9 (13.8%) | 6 (5.8%) | 5 (8.3%) |
| Obesity | 12 (7.1%) | 6 (9.2%) | 6 (5.8%) | 2 (3.3%) |
| Clinical chorioamnionitis | 10 (6.0%) | 5 (7.7%) | 5 (4.9%) | 8 (13.3%) |
| Meconium | 10 (6.0%) | 4 (6.2%) | 6 (5.8%) | 9 (15.0%) |
| Nonreassuring fetal heart tracing | 7 (4.2%) | 3 (4.6%) | 4 (3.9%) | 12 (20.0%) |
| Intrauterine growth restriction | 5 (3.0%) | 3 (4.6%) | 2 (1.9%) | 4 (6.7%) |
| Abruption | 4 (2.4%) | 1 (1.5%) | 3 (2.9%) | 3 (5.0%) |
| Zika virus exposure | 2 (1.2%) | 0 (0%) | 2 (1.9%) | 5 (8.3%) |
| Fetal/labor conditions | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3.3%) |
| None | 36 (21.4%) | 6 (9.2%) | 30 (29.1%) | 0 (0%) |
| In vitro fertilization | 45 (26.8%) | 12 (18.5%) | 33 (32.0%) | 0 (0%) |
| Placental size (percentile) | | | | |
| <10 | 49 (29.2%) | 21 (32.3%) | 28 (27.2%) | 29 (48.3%) |
| 11–50 | 57 (33.9%) | 21 (32.3%) | 36 (35.0%) | 19 (31.7%) |
| 51–90 | 40 (23.8%) | 15 (23.1%) | 25 (24.3%) | 10 (16.7%) |
| >90 | 22 (13.1%) | 8 (12.3%) | 14 (13.6%) | 2 (3.3%) |
| Umbilical cord coiling | | | | |
| Hypercoiled | 18 (10.7%) | 5 (7.7%) | 13 (12.6%) | 9 (15.0%) |
| Hypocoiled | 13 (7.7%) | 6 (9.2%) | 7 (6.8%) | 4 (6.7%) |
| Umbilical cord insertion | | | | |
| Peripheral | 7 (4.2%) | 3 (4.6%) | 4 (3.9%) | 3 (5.0%) |
| Marginal | 11 (6.5%) | 5 (7.7%) | 6 (5.8%) | 4 (6.7%) |
| Velamentous | 4 (2.4%) | 1 (1.5%) | 3 (2.9%) | 1 (1.7%) |
| Other umbilical cord findings | | | | |
| Single umbilical artery | 6 (3.6%) | 2 (3.1%) | 4 (3.9%) | 0 (0%) |
| True knot | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.7%) |
| Membrane insertion | | | | |
| Circummarginate | 4 (2.4%) | 4 (6.2%) | 0 (0%) | 4 (6.7%) |
| Circumvallate | 2 (1.2%) | 0 (0%) | 2 (1.9%) | 1 (1.7%) |

Abbreviations: GBS, group B strep; rAMA, regular advanced maternal age; vAMA, very advanced maternal age.

| Table 3. Histologic Findings of Overall Advanced Maternal Age (AMA) Group and AMA Age Subgroups | | | | |
|---|---|---|---|---|
| | Overall AMA Group, N = 168 | Age 35–39 (rAMA), N = 65 | Age ≥40 (vAMA), N = 103 | *P* Value (If Significant), (Age 35–39 Versus ≥40) |
| No significant histologic findings | 3 (1.8%) | 3 (4.6%) | 0 (0%) | |
| Meconium | 93 (55.4%) | 33 (50.8%) | 60 (58.3%) | |
| Maternal inflammatory response | 60 (35.7%) | 28 (43.1%) | 32 (31.1%) | |
| Stage 1 | 27 (16.1%) | 17 (26.2%) | 10 (9.7%) | |
| Stage 2 | 32 (19.0%) | 11 (16.9%) | 21 (20.4%) | |
| Stage 3 | 1 (0.6%) | 0 (0%) | 1 (1.0%) | |
| Fetal inflammatory response | 25 (14.9%) | 10 (15.4%) | 15 (14.6%) | |
| Stage 1 | 18 (10.7%) | 9 (13.8%) | 9 (8.7%) | |
| Stage 2 | 7 (4.2%) | 1 (1.5%) | 6 (5.8%) | |
| Stage 3 | 0 (0%) | 0 (0%) | 0 (0%) | |
| Villitis of unknown etiology | 45 (26.8%) | 14 (21.5%) | 31 (30.1%) | |
| Low grade | 24 (14.3%) | 9 (13.8%) | 15 (14.6%) | |
| High grade | 21 (12.5%) | 5 (7.7%) | 16 (15.5%) | |
| Fetal vascular malperfusion | 50 (29.8%) | 7 (10.8%) | 43 (41.7%) | .001 |
| Low grade | 33 (19.6%) | 2 (3.1%) | 31 (30.1%) | |
| High grade | 17 (10.1%) | 5 (7.7%) | 12 (11.7%) | |
| Maternal vascular malperfusion | 17 (10.1%) | 8 (12.3%) | 9 (8.7%) | |
| Grade 1 | 9 (5.4%) | 4 (6.2%) | 5 (4.9%) | |
| Grade 2 | 8 (4.8%) | 4 (6.2%) | 4 (3.9%) | |
| Placental infarct | 27 (16.1%) | 12 (18.5%) | 15 (14.6%) | |
| Multiple | 9 (5.4%) | 4 (6.2%) | 5 (4.9%) | |
| Intervillous thrombus | 47 (28.0%) | 12 (18.5%) | 35 (34.0%) | |
| Multiple | 16 (9.5%) | 7 (10.8%) | 9 (8.7%) | |
| Chorangiosis | 68 (40.5%) | 23 (35.4%) | 45 (43.7%) | |
| Delayed villous maturation | 14 (8.3%) | 1 (1.5%) | 13 (12.6%) | .02 |
| Villous edema | 14 (8.3%) | 3 (4.6%) | 11 (10.7%) | |
| Chronic deciduitis | 23 (13.7%) | 7 (10.8%) | 16 (15.5%) | |
| Plasma cell deciduitis | 11 (6.5%) | 6 (9.2%) | 5 (4.9%) | |
| Decidual arteriopathy | 10 (6.0%) | 1 (1.5%) | 9 (8.7%) | |
| Basal plate myometrial fibers | 14 (8.3%) | 2 (3.1%) | 12 (11.7%) | |

Abbreviations: rAMA, regular advanced maternal age; vAMA, very advanced maternal age.

The cases were further subdivided by age into regular AMA (rAMA; ages 35–39) and vAMA (greater than or equal to age 40). Of the total 168 cases, 65 (38.7%) were rAMA and 103 (61.3%) were vAMA. The average age in the rAMA subgroup was 37.1 and the median was 37. The average age in the vAMA subgroup was 41.9 and the median was 41. The average gravidity and parity were 2.8 and 2.2 for rAMA and 3.4 and 2.3 for vAMA, respectively.

Regarding the overall AMA cases, the most common clinical indications (aside from AMA) were maternal diabetes (20 of 168; 11.9%), hypertension or preeclampsia (16 of 168; 9.5%), Group B Streptococcus positivity (without treatment; 16 of 168; 9.5%), anemia or thrombocytopenia (including disorders, such as sickle cell trait/disease, von Willebrand disease; 15 of 168; 8.9%), and other maternal disease (which included most commonly prior myomectomy for fibroids, cholestasis, and thyroid disease; 15 of 168; 8.9%). Thirty-six cases (36 of 168; 21.4%; 6 rAMA and 30 vAMA) had no other clinical indication aside from AMA ("pure AMA" subgroup). The average gravidity of this group was 3.6 and the parity 2.5 (data not shown). In vitro fertilization was used in 26.8% (45 of 168) of cases. The majority of AMA placentas were 50th percentile for gestational age or less (106 of 168; 63.1%), with 29.2% (49 of 168) being less than 10th percentile for gestational age.

The clinical and gross findings of the non-AMA comparison group are also shown in Table 2. The average age of this group was 30.1 years and the median 31 years. The average gestational age at time of delivery was 39.1 weeks and the median 39 weeks. The clinical indications for placental histologic examination included the following: non-reassuring fetal status (12 of 60; 20.0%), grossly identified meconium-stained fluid (9 of 60; 15.0%), clinical chorioamnionitis (8 of 60; 13.3%), hypertension or preeclampsia (8 of 60; 13.3%), Zika virus exposure (5 of 60; 8.3%), intrauterine growth restriction (4 of 60; 6.7%), clinical diagnosis of abruption (3 of 60; 5.0%), gestational diabetes (2 of 60; 3.3%), obesity (2 of 60; 3.3%), fetal/labor conditions (2 of 60; 3.3%; 1 breech and 1 shoulder dystocia), and other maternal diseases/conditions (5 of 60; 8.3%; 1 mother with history of herpes simplex virus with active lesions, 1 with hepatitis C, and 3 with cholestasis). The majority of cases had placental sizes lower than the median for gestational age (48 of 60; 80.0%), with 48.3% (29 of 60) being less than the 10th percentile.

The histologic findings of the overall AMA group and the rAMA and vAMA subgroups are outlined in Table 3. The most common histologic finding, overall and for both age subgroups, was meconium deposition (93 of 168, 55.4% overall; 33 of 65, 50.8% rAMA; 60 of 103, 58.3% vAMA). Chorioamnionitis was another common histologic finding. While only 6% (10 of 168) of cases overall had noted clinical signs and symptoms of chorioamnionitis, 35.7% (60 of 168) of the AMA cases demonstrated acute chorioamnionitis histologically. These were divided roughly equally into Stage 1 and Stage 2 (27 of 168 [16.1%] and 32 of 168 [19.0%], respectively). Only a minority of cases showed Grade 2 severity inflammation (four cases total, three Stage 2 and one Stage 3; data not shown). When comparing the two age subgroups, while the rAMA group showed a higher frequency of chorioamnionitis (28 of 65; 43.1%) versus the vAMA subgroup (32 of 103; 31.1%), this finding did not reach statistical significance ($P = .28$). Overall, 14.9% (25 of 168) of cases showed a concomitant fetal inflammatory response component, the majority of which was Stage 1. The 2 subgroups showed a fetal inflammatory response in about equal frequency (10 of 65 [15.4%] rAMA and 15 of 103 [14.6%] vAMA, respectively). Villitis of unknown etiology (of any grade) was found in 26.8% (45 of 168) of cases overall, and in 21.5% (14 of 65) of rAMA and 30.1% (31 of 103) of vAMA cases, respectively. High-grade villitis of unknown etiology was found in 12.5% (21 of 168) of overall cases, 7.7% (5 of 65) of rAMA cases, and 15.5% (16 of 103) of vAMA cases. Maternal vascular malperfusion, which is an umbrella term encompassing varying pathologic alterations, including placental infarcts and decidual arteriopathy in addition to gross findings, such as small placenta size for gestational age and thin umbilical cord, was found in 10.1% (17 of 168) of the overall AMA cases, 12.3% (8 of 65) of the rAMA, and 8.7% (9 of 103) of the vAMA with no statistical difference between the 3 groups. Three cases total (3 of 168; 1.8%) showed no significant histologic findings, all of which were in the rAMA subgroup.

Two histologic findings were found to be significantly different in the 2 age subgroups (rAMA versus vAMA), FVM and delayed villous maturation. FVM was identified in 29.8% (50 of 168) of the overall AMA cases, with 19.6% (33 of 168) of cases being low grade in nature and 10.1% (17 of 168) high grade (compared with the non-AMA group where 45.0% [27 of 60] overall had FVM, 30.0% [18 of 60] of which was low grade and 15.0% [9 of 60] of which was high grade). Only 10.8% (7 of 65) of placentas in the rAMA subgroup group showed FVM (2 of 65 [3.1%] low grade, 5 of 65 [7.7%] high grade) while 41.7% (43 of 103) did in the vAMA subgroup (31 of 103 [30.1%] low grade, 12 of 103 [11.7%] high grade; $P = .001$). Delayed villous maturation was identified in 8.3% (14 of 168) of overall cases (compared with 5 of 60 [8.3%] of the non-AMA comparison group). Only 1 case in the rAMA subgroup (1 of 65; 1.5%) showed delayed villous maturation while 13 cases (13 of 103; 12.6%) did in the vAMA subgroup ($P = .02$).

Table 4 shows the histologic findings of the overall AMA group compared with pure AMA subgroup and to the non-AMA comparison group. The only statistically significant difference between the overall AMA group and non-AMA comparison group was the frequency of chronic deciduitis (30.0% [18 of 60] in the non-AMA comparison group versus 13.7% [23 of 168] in the overall AMA group; $P = .02$). There were no statistically significant differences between the pure AMA subgroup and either the overall AMA group or the non-AMA comparison group.

Of note, there were 2 cases of fetal demise (2 of 168; 1.2%). One case involved a 39-year-old woman who was at 24-weeks gestational age and the other case involved a 45-year-old woman at 28-weeks gestational age. Histologically, the case from the 39-year old showed multiple placental infarcts and high-grade FVM and the case from the 45-year old showed meconium deposition and low-grade FVM. The FVM in these cases were favored to be antemortem in nature due to spatial-temporal heterogeneity of the lesions.

## DISCUSSION

The number of women of advanced maternal age at the time of delivery is increasing due to a number of socioeconomic factors as well as being facilitated by the advancement of assisted reproductive technologies. As such, surgical pathologists will be receiving placenta specimens from these women with increasing frequency. While in the current literature there are many studies examining maternal and fetal outcomes in this population, relatively few studies to date have examined and detailed the histologic findings in their placentas. Thus, the goal of this study was to perform a detailed and comprehensive assessment of the histologic alterations in the placentas from this group of women to determine if there are any underlying recurrent histologic findings that may account for, or any histologic findings that may correlate with, the increase in adverse outcomes.

The most common histologic finding seen in our cases was meconium deposition. Slightly more than half of the cases (93 of 168; 55.4%) demonstrated meconium deposition on histologic review. Only 6% (10 of 168) of the cases noted meconium staining clinically. Meconium is fetal intestinal waste composed of intestinal secretions, mucus, and bile and excreted into the amniotic fluid. It has a controversial association with fetal distress in term pregnancies: while in the past it was largely thought to represent a fetal response to intrauterine stress and hypoxia, it is now recognized that meconium deposition may occur either with or without fetal insult,[44–48] and approximately 18% of term placentas demonstrate meconium staining.[49] Notably, the frequency of meconium deposition in both our overall AMA cases and pure AMA cases was not only much higher than that noted in the literature (93 of 168 [58.3%] and 21 of 36 58.3% versus approximately 18% noted in the literature), but was also comparable to our non-AMA "abnormal" placenta comparison group (30 of 60; 50.0%). However, the majority of cases demonstrated light to moderate meconium staining (were not extensive/diffuse). For this reason, in our view, meconium deposition in AMA placentas likely does not account for but may correlate with the increased adverse events documented in this population, serving more as an indicator that there are other underlying factors at work in these placentas that lead to intrauterine stress. In speaking to this point, other histologic findings that were relatively common in the AMA placentas, including FVM, have been noted to correlate with increased meconium deposition and may thus be contributing factors. However, this is far from a clear correlation as the etiology of meconium is so varied and may include processes ranging from intrauterine insult to inflammation/cytokine effect to physiologic defecation.

Fetal vascular malperfusion is a relatively recently introduced term established by the Amsterdam Interna-

**Table 4. Histologic Findings of Overall Advanced Maternal Age (AMA) Group, Pure AMA Subgroup, and Non-AMA Comparison Group**

| | Overall AMA Group, N = 168 | Pure AMA Subgroup, N = 36 | Non-AMA Comparison Group, N = 60 | *P* Value (If Significant), (Overall AMA Group to Non-AMA Comparison Group) |
|---|---|---|---|---|
| Placental size (percentile) | | | | |
| <10 | 49 (29.2%) | 9 (25.0%) | 29 (48.3%) | |
| 11–50 | 57 (33.9%) | 15 (41.7%) | 19 (31.7%) | |
| 51–90 | 40 (23.8%) | 7 (19.4%) | 10 (16.7%) | |
| >90 | 22 (13.1%) | 5 (13.9%) | 2 (3.3%) | |
| No significant histologic findings | 3 (1.8%) | 1 (2.8%) | 1 (1.7%) | |
| Meconium | 93 (55.4%) | 21 (58.3%) | 30 (50.0%) | |
| Maternal inflammatory response | 60 (35.7%) | 12 (33.3%) | 29 (48.3%) | |
| Stage 1 | 27 (16.1%) | 2 (5.6%) | 13 (21.7%) | |
| Stage 2 | 32 (19.0%) | 9 (25.0%) | 13 (21.7%) | |
| Stage 3 | 1 (0.6%) | 1 (2.8%) | 3 (5.0%) | |
| Fetal inflammatory response | 25 (14.9%) | 6 (16.7%) | 13 (21.7%) | |
| Stage 1 | 18 (10.7%) | 5 (13.9%) | 8 (13.3%) | |
| Stage 2 | 7 (4.2%) | 1 (2.8%) | 5 (8.3%) | |
| Stage 3 | 0 (0%) | 0 (0%) | 0 (0%) | |
| Villitis of unknown etiology | 45 (26.8%) | 11 (30.6%) | 17 (28.3%) | |
| Low grade | 24 (14.3%) | 5 (13.9%) | 10 (16.7%) | |
| High grade | 21 (12.5%) | 6 (16.7%) | 7 (11.7%) | |
| Fetal vascular malperfusion | 50 (29.8%) | 17 (47.2%) | 27 (45.0%) | |
| Low grade | 33 (19.6%) | 13 (36.1%) | 18 (30.0%) | |
| High grade | 17 (10.1%) | 4 (11.1%) | 9 (15.0%) | |
| Maternal vascular malperfusion | 17 (10.1%) | 4 (11.1%) | 11 (18.3%) | |
| Low grade | 9 (5.4%) | 3 (8.3%) | 6 (10.0%) | |
| High grade | 8 (4.8%) | 1 (2.8%) | 5 (8.3%) | |
| Placental infarct | 27 (16.1%) | 7 (19.4%) | 14 (23.3%) | |
| Multiple | 9 (5.4%) | 1 (2.8%) | 5 (8.3%) | |
| Intervillous thrombus | 47 (28.0%) | 13 (36.1%) | 19 (31.7%) | |
| Multiple | 16 (9.5%) | 5 (13.9%) | 6 (10.0%) | |
| Chorangiosis | 68 (40.5%) | 13 (36.1%) | 16 (26.7%) | |
| Delayed villous maturation | 14 (8.3%) | 5 (13.9%) | 5 (8.3%) | |
| Villous edema | 14 (8.3%) | 7 (19.4%) | 5 (8.3%) | |
| Chronic deciduitis | 23 (13.7%) | 5 (13.9%) | 18 (30.0%) | .02 |
| Plasma cell deciduitis | 11 (6.5%) | 3 (8.3%) | 9 (15.0%) | |
| Decidual arteriopathy | 10 (6.0%) | 1 (2.8%) | 5 (8.3%) | |
| Basal plate myometrial fibers | 14 (8.3%) | 3 (8.3%) | 5 (8.3%) | |

The pure AMA subgroup had no other clinical indications for pathologic examination aside from advanced maternal age. Of note, there were no statistically significant differences between the overall AMA group and the pure AMA subgroup, as well as no statistically significant differences between the pure AMA subgroup and the non-AMA comparison group.

tional Consensus group to describe a constellation of placental lesions that result from compromised fetal blood flow from a number of underlying etiologies that usually are fetal or placental in nature.[41] While the predominant risk factor is obstructed umbilical blood flow, there are other risk factors, including fetal hypercoagulability and processes causing vessel damage (such as from severe chronic villitis, acute chorioamnionitis with severe fetal inflammatory response, or meconium-associated myonecrosis).[50–52] The lesions described under the umbrella term of FVM include fetal vessel thrombosis, intramural fibrin deposition, avascular villi, villous stromal-vascular karyorrhexis, stem villous vessel obliteration, and vascular ectasia, and are further divided into high and low grade depending on both quantitative and qualitative measures.[41,50] FVM, particularly when high grade, has a strong association with poor fetal outcomes, which includes intrauterine fetal demise, intrauterine growth restriction, oligohydramnios, and cerebral events (cerebral palsy, stroke, hemorrhage).[50,51] FVM was identified in 29.8% (50 of 168) of our overall AMA cases and 47.2% (17 of 36) of our pure AMA cases, which is higher than published reports noting an incidence of anywhere from approximately 1% to 20% of unselected placentas.[53,54] Additionally, FVM was found in significantly higher frequency in the vAMA subgroup in comparison to the rAMA subgroup (43 of 103 [41.7%] versus 7 of 65 [10.8%]; $P = .001$). Of note, the majority of overall AMA cases with FVM were low grade in nature (33 of 168 [19.6%] low grade and 17 of 168 [10.1%] high grade), as well as both the pure AMA group (13 of 36 [36.1%] low grade, 4 of 36 [11.1%]

high grade) and the vAMA subgroup (3 of 103 [30.1%] low grade, 12 of 103 [11.7%] high grade). Thus, because the majority of FVM in the AMA cases was low grade in nature, this finding is of unknown clinical significance. However, the frequency of FVM within the overall AMA cases and the pure AMA cases was similar to the non-AMA comparison group (50 of 168 [29.8%] and 17 of 36 [47.2%] versus 27 of 60 [45.0%]), which again is a group that is selected for having some clinical indication for pathologic examination ("abnormal" placentas). It is conceivable that the finding of a relatively high frequency of FVM within the AMA population represents another finding correlating with the increased adverse outcomes in these pregnancies and there may be a complex interplay of underlying factors.

Another histologic finding that was found with increased frequency in the vAMA subgroup as compared with the rAMA subgroup was delayed villous maturation (13 of 103 [12.6%] versus 1 of 65 [1.5%]; $P = .02$). This was also found in relatively high frequency in the pure AMA group (5 of 36 [13.9%] versus 14 of 168 [8.3%] in the overall AMA group and 5 of 60 [8.3%] in the non-AMA comparison group). Delayed villous maturation has been associated clinically with varied maternal conditions, including maternal diabetes and obesity, as well as a number of adverse fetal outcomes, including perinatal demise, fetal growth restriction, and intrauterine hypoxia.[55–57] Although extrapolation of the incidence from published literature is difficult due to selection bias of the placentas examined (those that had an indication for pathologic examination), delayed villous maturation occurs in approximately 6% of pregnancies.[57] Given that FVM was found with higher frequency in the vAMA subgroup, these findings together could be an indication that there may be some degree of intrauterine hypoxia in this population. Notably, chorangiosis was also found with high frequency (68 of 168; 40.5%) in the overall AMA group as well as both age subgroups (23 of 65 [35.4%] and 45 of 103 [43.7%], respectively) and the pure AMA group (13 of 36; 36.1%), which were higher than the non-AMA comparison group (16 of 60; 26.7%), although it did not reach statistical significance. Although the exact pathogenesis is unknown, chorangiosis, which involves terminal villous hypervascularity, is thought to be an adaptive response to placental hypoxia and is related to a number of varied pregnancy risk factors, including maternal diabetes or anemia, chronic infections, cord abnormalities, fetal vascular thrombosis, multiple pregnancy, and stillbirth among others.[58] Again, this is far from a clear correlation and likely represents a complex interplay of different underlying factors.

A curious finding was that chronic deciduitis was found with decreased frequency in the overall AMA group compared with the non-AMA comparison group (23 of 168 [13.7%] versus 18 of 60 [30.0%]; $P = .02$). This finding was not associated with a statistically significant difference in villitis of unknown etiology between the 2 groups. This is an area that could potentially be explored in future studies.

There are limitations to this study, with one limitation being that we do not have a non-AMA "normal" comparison group. In our practice, we submit placentas for pathologic examination only if there is some indication necessitating as such, which broadly falls into the following 4 groups: maternal factors (such as AMA, diabetes, hypertension), placental factors (such as abruption, placental accreta, umbilical cord defects), fetal factors (such as nonreassuring tracings, small or large for gestational age, anomalies, intrauterine fetal demise), and pregnancy/labor/delivery variables (chorioamnionitis, manual extraction of placenta, preterm/postdates). Thus, our non-AMA comparison group is one of "abnormal" placentas, that is was enriched for cases where there conceivably are underlying confounders. In attempt to account for this, where relevant, the frequencies of each histologic findings from studies published in the literature are cited for comparison. Additionally, there are potential confounders not accounted for in our study population. For instance, race/ethnicity and body mass index are just some factors that may influence the placental findings. Although we made note of the race of our patient population and we accounted for clinically obese patients, the impact of race and body mass index specifically on the overall findings was not investigated. Another limitation to this study is that processes, such as delayed villous maturation, chorangiosis, and FVM, despite having definitions within the literature as guidelines, still have some subjectivity associated with them. In order to attempt to reduce this subjectivity, all cases were re-reviewed and strictly adhered to the definitions. Although the frequencies for alterations, including chorangiosis and FVM, were high in our cohort compared with the published frequencies in the literature, in our experience the minimum criteria for calling these alterations are met in many cases.

In conclusion, the finding of relatively high frequencies of FVM, delayed villous maturation, chorangiosis, and meconium deposition suggests, in our view, perhaps there is at least some component of intrauterine insult, such as hypoxia, that may be contributing to these findings, although this is far from a clear correlation and additional studies are needed. It is of interest, aside from chronic deciduitis, there were no significant differences between the non-AMA comparison group and the overall AMA group as well as the pure AMA subgroup. Thus, while the exact mechanism remains unclear, it does seem that AMA in of itself is an independent risk factor that is at least comparable to other common indications for placental examination. There is likely a complex interplay of different underlying factors that could account for the increased adverse events in pregnancies associated with AMA. We suggest AMA be another criteria for full pathologic examination of the placenta.

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