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The histologic evolution of revealed, acute abruptions

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Summary

There is considerable interest in using pathology to confirm acute abruptions. It has been suggested that pathologic findings can help to determine the timing of abruptions. Because of the dearth of evidence in the literature supporting this claim and its medicolegal implications, we undertook this study to explore further the possibility of timing abruptions by histopathology. We sought to correlate bleeding interval (duration from maternal presentation with vaginal bleeding (revealed abruption) to placental delivery) with placental histopathologic findings. We performed a retrospective review of clinical data and placental pathology from all cases of clinically-diagnosed, acute, revealed abruptions at a single, large institution in New England, between 2000 and 2015. Cases were identified based on clinical diagnoses, bleeding intervals were calculated from clinical notes, and histologic evaluations were performed by two pathologists blinded to the bleeding intervals. A total of 177 cases were analyzed. Of these, 103 (58%) had histologic findings corroborating the clinical diagnosis of abruption. The most frequent finding was maternal surface indentation (51 cases), followed by intravillous hemorrhage (50 cases). The former was also the earliest finding, with a minimum bleeding interval of 4 minutes. In multivariate modeling, plasma cell deciduitis was significantly associated with a longer bleeding interval (median 63 hours). If there were two pathologic findings, there was a trend toward a longer bleeding interval. There was modest sensitivity for the pathologic diagnosis of acute revealed abruption. Although there was not a clear, step-wise progression of histologic lesions, the presence of two or more findings tended to be seen with longer bleeding intervals. Our results suggest that histologic findings cannot be used to time acute revealed abruptions reliably and any interpretation of such should be made with caution.

Keywords

acute abruption; placenta; retroplacental hematoma; chorioamnionitis; decidual inflammation

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Introduction

Placental abruption, defined as the premature separation of the placenta from the decidua at or after 20 weeks gestation, complicates 1–2% of pregnancies in the United States [1,2]. Placental abruption has been associated with a 9- to 10-fold increase in the risk of stillbirth, with the majority of perinatal mortality attributable to preterm delivery. It has been estimated that 20–40% of placental abruptions end in preterm delivery [2], as rates of abruption peak between 24 and 26 weeks [3]. Additional associated adverse perinatal outcomes include an increased risk of cystic periventricular leukomalacia, intraventricular hemorrhage, and cerebral palsy [3–7]. Maternal complications include hemorrhage, need for hysterectomy, disseminated intravascular coagulation, and death [3,8].

Placental abruption is a clinical diagnosis, typically characterized by vaginal bleeding, abdominal pain, uterine contraction and/or tenderness, and sometimes non-reassuring fetal monitoring [3,9,10]. Although clinicians may regard placental abruption as an acute phenomenon, there is growing evidence to support that in many cases, it is a long-standing process, with contributions from abnormal trophoblast invasion and remodeling of spiral arteries as well as chronic inflammation [10,11]. The etiology of placental abruption remains enigmatic; however, a combination of acute and/or chronic processes have been identified as risk factors, including but not limited to premature rupture of membranes (PROM), intrauterine infection, hypertension and/or pre-eclampsia, and cigarette smoking [1,3,10,12–15]. The greatest risk factor for abruption is a history of a prior abruption [1,16].

The pathologic diagnosis of placental abruption is fairly well established. It is generally accepted that gross findings consistent with abruption include retroplacental blood or clot with underlying parenchymal indentation [9,17–22]. Nonspecific histologic features are often present with a clinical diagnosis of abruption and are considered supportive or suggestive of abruption, including hemorrhage dissecting through the decidua [20], intravillous and/or intervillous hemorrhage [9,17,19,20,22], early trophoblastic necrosis [9,20,22], decidual inflammation [15,18,20], and acute chorioamnionitis [9,17,23]. Interestingly, the incidence of histologic acute abruptions is greater than – approximately double – the incidence of clinically diagnosed acute abruptions [3]. It has been noted that the majority of these clinically silent histologic acute abruptions have unremarkable obstetric histories and may not have clinical consequences [3].

Despite the potential unreliability of a pathologic diagnosis of acute placental abruption, there remains considerable interest in using pathology in a confirmatory capacity [9,20,21,23–25]. Based on a series of stillborn autopsies with retroplacental hematoma/hemorrhage, it has even been suggested that pathology may be able to time abruptions [20]. Assuming acute asphyxia caused by acute placental abruption as the cause of death, Bendon correlated histologic features of abruption with published criteria for intrauterine duration of retention of a fetal death [26,27]. He found basal plate neutrophils present in all cases and suggested it developed within 1–4 hours of abruption/death. Bendon found that early coagulative necrosis, particularly characterized by smudging and/or paleness of syncytiotrophoblastic nuclei, developed over and nearly completed by 24 hours [20]. There are serious medicolegal implications to the claim that pathologic examination can determine

when an abruption happened. Because of the relative paucity of studies describing the pathologic features of acute abruption in terms of timing, we undertook this study to explore further the possibility of timing abruptions by histopathology.

Materials and Methods

This study was performed at Massachusetts General Hospital (MGH) with Institutional Review Board approval. The MGH pathology laboratory information system was queried for all cases of clinically diagnosed or suspected acute abruption in 2000–2015, yielding 236 cases. From this pool we included only revealed, acute abruptions with documented maternal vaginal bleeding episode(s) within 1 week of delivery of liveborn infants, netting 177 cases. These abruptions were clinically diagnosed based on the presence of symptoms such as abdominal pain, uterine tenderness or hypertonicity, or nonreassuring fetal status in addition to bleeding per vagina, which was an inclusion criterion. Exclusion criteria were lack of documented bleeding interval, stillbirth, most recent bleeding episode greater than 1 week before delivery, and suspected or confirmed placenta previa (complete, partial, or resolved previas were all excluded). We also excluded all non-abruption potential sources of vaginal bleeding that could be discerned, for example: membranous insertion of the umbilical cord, membranous vessels, and crotas. We included cases with multiple gestations, congenital anomalies, and neonatal deaths.

Clinical bleeding interval was defined as the duration of time between maternal presentation with vaginal bleeding and delivery of the placenta and was calculated from the medical records for each case. When cases had multiple bleeding episodes, we recorded the bleeding interval for the most recent bleeding episode only. Data pertaining to maternal risk factors for acute abruption and infants' gestational ages and APGAR scores at 1 minute and 5 minutes were abstracted from the medical records as well (Table 1).

At the MGH all placentas from in house deliveries and transfers from outside institutions to the MGH NICU are received in the pathology department and then triaged either for placental examination or refrigerated storage for approximately two weeks (retrieving placental from late NICU admissions or maternal re-admissions). Criteria for full pathological examination are based on exclusion: all placentas are examined except for term singletons without maternal, obstetric, fetal, or neonatal complications. All placentas are examined fresh by trained pathology assistants, supervised pathology residents, or perinatal pathologists. One of the authors (D.J.R.) has personally trained or supervised these individuals. The MGH uses a template approach for gross examination of the placenta to ensure a reproducible examination (available upon request). After a detailed gross examination, including evaluation for maternal surface hemorrhage/clot and/or indentation/compression, representative sections are submitted as per generally established guidelines [17,18,19,22], including at least one each of cord and membranes and 2–3 sections of parenchyma with fetal and maternal surfaces. Lesions, such as retroplacental hematomas, infarcts, or otherwise abnormal-appearing parenchyma, are also sampled. All blocks are fixed in 10% buffered formalin for at least 4 hours and then submitted for routine histology (automatic processing, embedding in paraffin, and obtaining 5 µm cut sections resulting in hematoxylin and eosin-stained slides).

Glass slides for all 177 cases were retrieved from storage in the pathology archives. All cases were retrospectively reviewed by D.J.R. and A.L.C. independently and scored for the presence or absence of the following gross and histologic findings: grossly identified maternal surface indentation and/or histologically identified villous compression; intravillous hemorrhage; acute inflammation, including acute chorioamnionitis, with or without fetal inflammatory response, and neutrophils in the retroplacental clot, decidua, intervillous space, and/or membranes in or near the area of the hematoma; trophoblastic ischemic changes not frank infarction, such as nuclear smudging, loss of nuclear basophilia, and karyorrhexis; infarction and/or fibrin deposition in the area of the abruption, and plasma cell deciduitis (Table 2; Figures 1,2, 3, and 4). Cases with discrepant diagnoses were re-reviewed together for a consensus diagnosis.

To determine specificity of the findings for abruption we attempted to formulate a control cohort. Two hundred and one placentas submitted for full pathologic examination for non-abruption, non-previa, and otherwise non-bleeding related reasons were selected at random from the pathology archives at MGH. Any maternal history of bleeding or pathological findings that may predispose to bleeding during pregnancy (e.g. placental previa, velamentous cord insertion, cetas, manual extraction of the placenta) was reason for exclusion, and again, stillbirths were excluded. Pathology reports for these placentas were evaluated for the presence or absence of the same gross and histologic findings listed above. The demographics of this population are presented in Table 3. Diagnoses of these control placentas, alongside those of the abruption placentas, are tabulated in Table 4.

Continuous outcomes were summarized by mean ($\pm$ standard deviation) or median (and interquartile range) and categorical outcomes by counts (%). Unpaired two-tailed t-test was used to compare the ages and gestational ages of the mothers in the abruption and control cohorts, while Wilcoxon rank sum test was used to compare the parities. Fisher's exact test was used to compare the prevalences of the findings in the two groups. Multivariate general linear model was used to determine which if any of the findings was significantly associated with shorter or longer bleeding intervals using JMP Pro 12 software (SAS, Cary, NC). Additionally, Wilcoxon rank sum test was used to compare the bleeding intervals associated with the presence or absence of the scored pathologic findings, singly or in specific combinations with other findings. P-values <0.05 were considered significant.

Results

Only one of the 201 control cases had gross and histologic findings suggestive of abruption (maternal surface indentation with an intraparenchymal hematoma with associated infarction), but there was not a known history of maternal bleeding during pregnancy. Possibly this was a hidden (concealed) abruption. Including this case, the controls' mean age was 35.6 (± 5.9) years (range 17–50), mean gestational age was 38.2 (± 3.0) weeks (range 21.7–41.9) and the mean parity of the mothers was 1.0 (± 1.1 ; range 0–6).

There were 177 acute abruptions that met inclusion criteria. Two-thirds of cases (117, 66%) had bleeding intervals ≤ 1 day, with the majority (113, 64%) ≤ 12 hours. Figure 5 illustrates the distribution of bleeding intervals. The mean age was 30.0 (± 6.3) years (range 14–45),

mean gestational age was 34.5 (± 4.8) weeks (range 21.1–41.0), and the mean parity of the mothers was 0.9 (± 1.2 ; range 0–5). While the maternal age and gestational age of cases diagnosed with abruptions were significantly less than that of the control group ($p < 0.001$), there was not a difference in parity between the two groups ($p = 0.34$). Table 3 compares the demographic data for the control and abruption cohorts. There were significantly more placentas in the abruption cohort with maternal surface indentation (29% vs. 3%, $p < 0.001$), intravillous hemorrhage (28% vs. 3%, $p < 0.001$), trophoblastic ischemic changes (15% vs. 0.5%, $p < 0.001$), and infarction and/or fibrin deposition in the area of maternal surface indentation or intravillous hemorrhage (16% vs. 1%). There was no difference between the abruption and control groups for acute inflammation (24% vs. 20%, $p = 0.38$) or plasma cell deciduitis (6% vs. 4%, $p = 0.48$). Exact p values are provided in Table 4.

Seven deliveries in the abruption cohort resulted in 8 neonatal deaths; one was a twin delivery at 21.1 weeks where both twins died (Table 5). Except for 2 cases (33.9 and 34 weeks gestational age), most were extreme preterm deliveries (5 cases between 21.1–24.3 weeks gestational age). The risk factors for these seven abruptions included PROM/preterm PROM (PPROM), high parity, and twin gestation. Bleeding intervals were clustered in the 3–5 hour range, but 3 cases had bleeding intervals of 22 hours, 48 hours, and 96 hours. Histologic findings supportive of a diagnosis of abruption were seen in five of these seven deliveries that resulted in neonatal deaths, with intravillous hemorrhage most frequent.

Forty-two cases of acute abruption (24%), 6 term and 36 preterm, had documented clinical risk factors for abruption (Table 6). Six women (3%) had more than one risk factor. The most frequent risk factors noted were PROM/PPROM (12), cigarette smoking (10), multiple gestation (9), and hypertension and/or pre-eclampsia (9). Only two women (1%) had a history of a prior abruption. Both of their placentas were positive for pathologic findings supporting the diagnosis of acute abruption (diagnoses listed in Table 2). In contrast, placentas from the other 40 women with risk factors had scored pathologies 50–67% of the time (for risk factors with more than 2 cases each).

Overall, 103 (58%) of the 177 cases of acute abruption were histologically supported by the presence of at least one of the pathologies listed in Table 2. On the other hand, 74 cases (42%) had no gross or histopathologic findings. The histogram in Figure 6 illustrates frequency of pathologic findings per case. The median bleeding intervals of the positive and negative cases were 6 hours (interquartile range 1.7–21.8 hours) and 8.3 hours (interquartile range 2.3–17 hours), respectively ($p = 0.94$). There were significantly more preterm deliveries in the pathology positive group compared to the pathology negative group. The average gestational age of the positive cases was 33.6 weeks, for a 67% preterm delivery rate, compared to 35.9 weeks and a 54.1% preterm rate for the negative cases ($p = 0.002$).

If there were findings, the earliest finding was maternal surface indentation with or without histologically confirmed villous compression, present by 4 minutes (median 5.5 hours; interquartile range 1.8–20 hours), followed by intravillous hemorrhage, at 8 minutes (median 8 hours; interquartile range 2.8–30 hours). In multivariate analysis of all six histopathologic findings, plasma cell deciduitis was associated with longer bleeding intervals (median 63 hours with interquartile range 3–78 hours; $p < 0.001$). Table 7 details the median, earliest, and

interquartile range of bleeding intervals for each of the pathologic findings. The earliest bleeding interval for the pathology negative cases was 1 minute, with a range from 1 minute to 6.5 days.

If there were two histopathologic findings, the bleeding interval tended to be longer, although often this was not significant. For example, finding acute inflammation in addition to intravillous hemorrhage lengthened the bleeding interval associated with intravillous hemorrhage significantly, from a median of 8 hours to 44.5 hours ($p=0.005$). On the other hand, finding infarction or fibrin deposition in the area of the abruption seemed to lengthen the bleeding interval associated with intravillous hemorrhage, to 23 hours; however, this was not significant ($p=0.06$). Table 8 lists combinations of findings and the median, earliest, and interquartile range of bleeding intervals.

Comments

We found that histologic findings supporting the clinical diagnosis of acute abruption, with delivery within 1 week of maternal presentation with bleeding, had a sensitivity of 58%. Our results are comparable to the results of a large case-control study by Elsasser *et al*, in which they calculated a sensitivity of 30.2% and a specificity of 100% [9]. Elsasser *et al* suggest that the most common pathologic finding associated with the clinical history of abruption is retroplacental clot [9]. There is significant subjectivity, however, in describing the presence of retroplacental clots (and underlying maternal surface indentation) by our obstetrician colleagues and/or pathologists or pathology assistants; thus we restricted our analysis to revealed cases, *i.e.*, cases with documented antenatal bleeding. The histologic findings scored – grossly evident maternal surface indentation with or without underlying histologically confirmed villous compression, intravillous hemorrhage, acute inflammation, trophoblastic ischemic changes, infarction and/or fibrin deposition, and plasma cell deciduitis – were chosen based on literature [9,15,17–20,22,23] as well as the senior author's (D.J.R.'s) personal experience. These diagnoses have a subjective component which is unavoidable. We acknowledge that this is a dilemma but it is so in much of placental pathology that has no reported nosology. We tried to be as objective as possible in all diagnoses using strict pathological definitions and requiring consensus diagnoses.

Additionally, we found, as have others [9,21,23], that some placental findings are fairly commonly associated with revealed abruptions, suggesting possible mechanisms. For example, acute inflammation was present in 43 of our 177 cases (24%), and seen at a median bleeding interval of 8 hours. This finding was noted in 7 of the 12 cases (58%) with PROM/PPROM documented as a risk factor for acute abruption. Thus we agree with Nath *et al*, Elsasser *et al*, and Heller *et al*, that inflammation itself is likely a risk factor facilitating abruption [9,21,23]. Interestingly, our results suggest that acute inflammation is associated with some chronicity to the acute abruption, as it was not the earliest feature seen (maternal surface indentation and intravillous hemorrhage were both seen earlier). Acute inflammation, specifically acute chorioamnionitis, was present in 41 control cases (20%, $p=0.38$), however, leading us to believe that as a histologic finding it is only supportive of a diagnosis of acute abruption and needs other confirmatory findings. The same is true for

plasma cell deciduitis, which we identified in 4% of the controls and 6% of the abruptions (p=0.48).

When we subcategorized the acute inflammation in the 43 cases as acute inflammation seen in the decidua (hereafter referred to as Bendon's basal neutrophils [20]), acute inflammation seen in the hemorrhage/hematoma or intervillous space in the abrupted area, or the acute inflammation of acute chorioamnionitis, we found that a median bleeding interval of 420 min (interquartile range 210–1199.5 min) for 27 cases showing acute chorioamnionitis, 930 min (interquartile range 202.5–3855 min) for 10 cases with Bendon's basal neutrophils, and 900 min (interquartile range 270–4320 min) for 17 cases with an acute inflammatory infiltrate in the abrupted area. ANOVA on ranks did not detect a significant difference between these groups (p=0.27). Wilcoxon rank sum test between acute chorioamnionitis versus all other acute inflammation also did not detect a significant difference (p=0.22). Although one could suspect that the timing of acute chorioamnionitis is different and likely earlier than the appearance of Bendon's basal neutrophils and neutrophils in the abruption, our study is underpowered to confirm such a conjecture.

Our data is skewed to very early revealed, acute abruptions, as most of our cases had bleeding intervals within 12 hours of delivery (113/177, 64%). Although we had hoped to find a step-wise index of pathologic findings correlating to the timing of the abruption, our data failed to demonstrate such a linear progression of features. This may be because the cases we reviewed were all revealed abruptions. It seems logical that for many pathologic features to develop, the pressure/mass effect of abruption must be present. The fact that these abruptions bled (were revealed) likely decreased this effect and therefore may have resulted in the relative paucity of findings. This is highlighted by the absence of ANY pathologic findings in 42% of our cases, meaning that they were pathologically invisible abruptions. This should bring pause to perinatal pathologists trying to confirm a clinical diagnosis of revealed, acute abruption. Especially in this litigious era, placental pathology findings may have important medicolegal implications. Our results suggest that one cannot accurately time a revealed abruption based on pathologic findings. We urge pathologists to be cognizant of the subjectivity involved in these diagnoses as well and encourage adherence to strict pathologic definitions. Absence of pathologic findings does not rule out placental abruption, which remains best a clinical diagnosis.

In our study, the presence of histologic findings does seem to corroborate the diagnosis, but we did not see a clear, step-wise evolution of lesions over time. The presence of more than one pathologic finding tended to be seen with longer bleeding intervals, but few specific combinations of findings reached statistical significance. Even when we segregated pathology positive cases into groups based on timing of findings (acute, sub-acute to chronic, and mixed) ANOVA on ranks did not detect a significant difference (p=0.20). We grouped acute pathologies only (indentation/villous compression, intravillous hemorrhage, mild, low-stage and low-grade acute chorioamnionitis; median bleeding interval 240 min with interquartile range 120–555 min), subacute/chronic pathologies only (more severe acute chorioamnionitis, Bendon's basal neutrophils, neutrophils in the area of abruption, trophoblastic ischemic changes, infarction/fibrin deposition, plasma cell deciduitis; median bleeding interval 690 min with interquartile range 273.75–990 min), and mixed acute and

subacute/chronic pathologies (median bleeding interval 435 min with interquartile range 119.25–2775 min). Similar to prior reports, we found that acute abruption may develop in the setting of chronic conditions, *e.g.*, plasma cell deciduitis, and some acute conditions, *e.g.*, acute inflammation, may have a degree of chronicity to them.

There are several limitations of our study. One is observation bias; there is a level of subjectivity in the diagnosis of abruption and its chart documentation. We relied on clinical notes, which may be incomplete or contain data transcription errors, to calculate bleeding intervals and for risk factor documentation. Despite our moderately large sample size, there is still the possibility of a Type II error, and we were unable to perform statistical analyses on any clinical risk factors due to limited power. We included multiple gestations and included in the analysis the disc which showed histologic findings. We excluded stillbirths, as we felt that involution artifact could complicate our data [28]. On the other hand, we included cases of neonatal deaths – the majority of which were extreme preterm deaths.

In summary, our findings suggest that in revealed, acute abruptions, pathologic features supporting the diagnosis are present in more than half of cases but a significant number were pathologically silent. Our findings posit that in revealed acute abruptions there is not a pathologic time course to date these abruptions. We found that our categories of pathology are best in the hours to one day range. Some features that have been associated with very acute intervals (minutes) can be seen over much longer time frames; *e.g.*, intravillous hemorrhage was still seen up to 1 week after the abruption was revealed. The only finding that was significant for longer intervals was plasma cell deciduitis, although it was not unique to acute abruptions (it was identified in 4% of control placentas).

We chose to analyze revealed abruptions only, because we could estimate the bleeding interval based on clinical notes. We would be cautious in generalizing our findings to all abruptions or concealed abruptions. Our results may serve as a template on which to base further studies, potentially including concealed abruptions using ultrasound imaging to document timing.

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Figure 1.
Retroplacental clot, indenting the underlying maternal surface. The bleeding interval was 119 minutes.

Figure 2.

Whole mount (a. H&E, 1X) and intermediate-power (b. H&E, 200X) photographs of the histologic section corresponding to the gross photograph in Figure 1. The clot was non-adherent as evident in the whole mount photograph. Underlying parenchymal changes were present, however, as seen in the microscopic photo of the boxed area showing intravillous hemorrhage and trophoblastic ischemic changes.

Figure 3. Abruptio with bleeding interval of 2460 minutes. The low-power (a. H&E, 100X) photograph demonstrates an area of intravillous hemorrhage, mild acute inflammation, trophoblastic ischemic changes (nuclear smudging and loss of basophilia), and early fibrin deposition. The higher-power (b. H&E, 200X) photograph illustrates hemorrhage dissecting through the decidua, with decidual (basal plate) neutrophilic inflammation.

Figure 4. Abruptio with bleeding interval of 3780 minutes. At low power (a. H&E, 100X), basal chronic villitis is evident. At high power (b. H&E, 400X), the presence of increased plasma cells, consistent with plasma cell deciduitis, is confirmed. This placenta also showed intravillous hemorrhage, acute inflammation in the area of the abruption and chorioamnionitis, and infarction (not shown).

Figure 5.

Histogram of duration of maternal bleeding prior to delivery of placenta, for all acute abruptions (n=177).

Figure 6.
Histogram of pathologic findings per case, for all acute abruptions (n=177).

Table 1

Clinical risk factors for abruption [1,3,10,12–15].

High parity (≥ 5) [3,15]
Multiple gestation [3]
Cigarette smoking [3,14,15]
Cocaine use [3,15]
Trauma (including domestic abuse) [3,10,14]
Hypertension and/or pre-eclampsia [1,3,12,14,15]
Premature rupture of membranes or prolonged premature rupture of membrane [1,3,13,15]
History of prior abruption [1,10,14,15]
Other (e.g., uterine rupture, abnormal uterine placental implantation) [10]

Table 2

Histologic findings scored.

Histologic finding scored:	Criteria [17–19,22]:
Maternal surface indentation and/or villous compression	Gross examination – Measurable indentation of the placental parenchyma with associated retroplacental hemorrhage. Histologic examination – an area of parenchyma with significant decrease in the amount of intervillous space, without “agglutination [29]” or associated intervillous or retroplacental hemorrhage.
Intravillous hemorrhage	“Bag of blood” morphology – red blood cells loose within the villous stroma, typically striking even at low power.
Acute inflammation	Acute chorioamnionitis or marked numbers of inflammatory cells in the hematoma or decidua associated with the hematoma (the latter as described by Bendon [20]).
Trophoblastic ischemic changes	Syncytiotrophoblast nuclear smudging (loss of nuclear detail), loss of nuclear basophilia, and/or karyorrhexis.
Infarction and/or fibrin deposition	Infarction – localized ischemic villous necrosis, with villous “agglutination” and varying degrees of villous stromal degeneration and trophoblastic ischemic changes (as above) associated with intervillous or retroplacental hemorrhage. Fibrin deposition – acellular, eosinophilic material, presumed derived from the maternal blood, in the intervillous space, typically around the periphery of an infarct and in association with intervillous or retroplacental hemorrhage.
Plasma cell deciduitis	Lymphoplasmacytic infiltrate of at least 5 plasma cells in the decidua, visible at 2–4x, often accompanied by basal chronic villitis.

Table 3

Comparison of the control vs. abruption cohorts.

Parameter compared	Control group	Abruption group	P-value
Maternal age	35.6 ($\pm$ 5.9) years	30.0 ($\pm$ 6.3)	6.15e-17 ^b
Gestational age	38.2 ($\pm$ 3.0) weeks	34.5 ($\pm$ 4.8) weeks	3.23e-16 ^b
Parity	1.0 ($\pm$ 1.1)	0.9 ($\pm$ 1.2)	0.34
Indication for placental examination ^a	Maternal: 57/201 (28%) Fetal: 80/201 (40%) Obstetric: 71/201 (34%) Placental: 23/201 (11%)	Obstetric: 177/177 (100%)	N/A

^aAll placentas from the abruption group were submitted to the pathology department for examination because of the clinical diagnosis of abruption (obstetric indication). For the control group, maternal indications include the following: chronic hypertension, advanced maternal age, other maternal disease, Zika virus exposure, other maternal infections or exposures (not including acute chorioamnionitis), obesity, and tobacco or other substance use or abuse; fetal indications for examination include the following: intrauterine growth restriction, macrosomia, Trisomy 21, meconium, infant admission to the NICU, prematurity, non-reassuring fetal monitoring/testing, decreased fetal activity, and fetal dysrhythmia; obstetric indications for examination include the following: gestational diabetes, gestational hypertension, acute chorioamnionitis, pre-eclampsia/toxemia, HELLP syndrome or gestational thrombocytopenia, extramural delivery, oligo- or polyhydramnios, history of prior stillbirth, unstable lie, and peripartum cardiomyopathy; and placental indications for examination include the following: single umbilical artery, incomplete placenta, manual extraction, accessory lobe, varix, and fibroids. Percentages add up to greater than 100% as some placentas were sent for more than one indication.

^bDenotes a significant p-value.

Table 4

Prevalence of findings in the control vs. abruption cohorts.

Histologic finding	Control group	Abruption group	P-value
Maternal surface indentation and/or villous compression	7 (3%)	51 (29%)	1.9e-12 ^b
Intravillous hemorrhage	6 (3%)	50 (28%)	8.5e-13 ^b
Acute inflammation	41 (20%)	43 (24%)	0.38
Trophoblastic ischemic changes	1 (0.5%) ^a	27 (15%)	6.68e-9 ^b
Infarction and/or fibrin deposition	2 (1%) ^a	28 (16%)	2.8e-8 ^b
Plasma cell deciduitis	8 (4%)	10 (6%)	0.48

^a Slides for the control cases with infarction and/or fibrin deposition were re-reviewed and trophoblastic ischemic changes were present in one of the two cases.

^b Denotes a significant p-value.

Table 5

Clinical risk factors and placental findings for seven neonatal deaths.

Case presentation:	Clinical risk factors:	Histologic findings:
Maternal bleeding for 5 h, delivery at 34 weeks gestational age (GA)	PROM/PPROM ^a	Acute chorioamnionitis
Maternal bleeding for 48 h, delivery at 23.1 weeks GA	None	Maternal surface indentation/villous compression, intravillous hemorrhage, acute inflammation in the area of the abruption
Maternal bleeding for 4 h, delivery at 23.9 weeks GA	High parity (5)	Intravillous hemorrhage (IVH)
Maternal bleeding for 3 h, delivery at 24.3 weeks GA	None	IVH
Maternal bleeding for 96 h, delivery at 33.9 weeks GA	None	None
Maternal bleeding for 22 h, delivery at 21.1 weeks GA	Twin pregnancy	None
Maternal bleeding for 4 h, delivery at 22 weeks GA	None	IVH

^aPROM/PPROM = Premature rupture of membranes/preterm premature rupture of membranes.

Table 6

Frequency of clinical risk factors and their associated placental findings.

Clinical risk factor:	Number of cases ^b :	Histologically-confirmed acute abruptions:	Pathologic findings:
High parity (5)	4	2	1 case with indentation/villous compression, acute inflammation (AI; in the area of the abruption), trophoblastic changes, infarct/fibrin 1 case with intravillous hemorrhage (IVH)
Multiple gestation	9	6	1 case with IVH, trophoblastic changes, infarct/fibrin, and plasma cell deciduitis 1 case with IVH and acute chorioamnionitis 1 case with indentation/villous compression and IVH 2 cases with IVH 1 case with acute chorioamnionitis
Cigarette smoking	10	6	1 case with indentation/villous compression, trophoblastic changes, and infarct/fibrin 1 case with indentation/villous compression, IVH, and AI (in the area of the abruption) 1 case with indentation/villous compression, IVH, trophoblastic changes, and infarct/fibrin 1 case with indentation/villous compression and IVH 1 case with IVH 1 case with acute chorioamnionitis
Cocaine use	5	4	2 cases with acute chorioamnionitis 1 case with indentation/villous compression, AI (in the area of the abruption), trophoblastic changes, and infarct/fibrin 1 case with indentation/ compression and IVH
Motor vehicle accident	1	0	None
Hypertension and/or pre-eclampsia	9	6	1 case with indentation/villous compression, IVH, and trophoblastic changes 1 case with indentation/villous compression, AI (basal/decidual and in the area of the abruption), trophoblastic changes, infarct/fibrin, and plasma cell deciduitis 1 case with indentation/villous compression, IVH, trophoblastic changes, and infarct/fibrin 1 case with indentation/villous compression and IVH 1 case with indentation/villous compression and trophoblastic changes 1 case with acute chorioamnionitis
PROM/PPROM ^a	12	7	4 cases with acute chorioamnionitis 1 case with AI (basal/decidual and in the area of the abruption)

Clinical risk factor:	Number of cases ^b :	Histologically-confirmed acute abruptions:	Pathologic findings:
			1 case with IVH and acute chorioamnionitis 1 case with indentation/villous compression, IVH, AI (basal/decidual and in the area of the abruption), trophoblastic changes, infarct/fibrin, and plasma cell deciduitis
Prior abruption	2	2	1 case with indentation/villous compression, AI (in the area of the abruption), trophoblastic changes, and infarct/fibrin 1 case with IVH
Uterine rupture	1	1	1 case with indentation/villous compression and IVH
Domestic violence	1	0	None

^aPROM/PPROM = Premature rupture of membranes/preterm premature rupture of membranes.

^bOf the 42 cases with at least one clinical risk factor for abruption, 6 had more than one risk factor. These were: 1 case of cigarette and cocaine use, 1 case of cigarette and cocaine use plus hypertension/pre-eclampsia and PROM/PPROM, 1 case of hypertension/pre-eclampsia and PROM/PPROM, 1 case of multiple gestation with hypertension/pre-eclampsia, and 2 cases of multiple gestation with PROM/PPROM.

Table 7

Bleeding intervals for histologic findings compatible with or supportive of the clinical diagnosis of acute abruption.

Histologic finding:	Number of cases:	Earliest bleeding interval:	Median bleeding interval:	Interquartile range:
Maternal surface indentation and/or villous compression	51	4 min	330 min (5.5 h)	109.5–1200 min (1.8–20 h)
Intravillous hemorrhage	50	8 min	480 min (8 h)	168.8–1800 min (2.8–30 h)
Acute inflammation ^a	43	10 min	480 min (8 h)	210–2010 min (3.5–33.5 h)
Trophoblastic ischemic changes	27	30 min	360 min (6 h)	104.5–1920 min (1.7–32 h)
Infarction and/or fibrin deposition	28	10 min	360 min (6 h)	165–2790 min (2.8–46.5 h)
Plasma cell deciduitis	10	10 min	3780 min (63 h)	180–4680 min (3–78 h)

^aOf the 43 cases with acute inflammation, 27 showed acute chorioamnionitis (median 420 min; interquartile range 210–1199.5 min), 10 had basal/decidual neutrophils (median 930 min; interquartile range 202.5–3855 min), and 17 had an acute inflammatory infiltrate in the abruption (median 900 min; interquartile range 270–4320 min). ANOVA on ranks did not detect a significant difference between these groups (p=0.27). Wilcoxon rank sum test between acute chorioamnionitis versus all other acute inflammation also did not detect a significant difference (p=0.22).

Table 8

Bleeding intervals for more than one histologic finding of acute abruption.

Finding #1:	Finding #2:	Median bleeding interval:	Earliest bleeding interval:	Interquartile range:
Maternal surface indentation and/or villous compression (MSI/VC)	None or any	330 min (5.5 h)	4 min	109.5–1200 min (1.8–20 h)
MSI/VC	Intravillous hemorrhage (IVH)	390 min (6.5 h)	30 min	180–2460 min (3–41 h)
MSI/VC	Acute inflammation (AI) ^a	720 min (12 h)	10 min	180–4320 min (3–72 h)
MSI/VC	Trophoblastic ischemic changes	360 min (6 h)	30 min	119.8–2925 min (2.0–48.8 h)
MSI/VC	Infarction and/or fibrin deposition	315 min (5.3 h)	10 min	165–2925 min (2.8–48.8 h)
MSI/VC	Plasma cell deciduitis	4320 min (72 h) ^b	270 min	2295–6480 min (38.3–108 h)
IVH	None or any	480 min (8 h)	8 min	168.8–1800 min (2.8–30 h)
IVH	AI ^a	2670 min (44.5) ^c	90 min	810–4320 min (13.5–72 h)
IVH	Trophoblastic ischemic changes	900 min (15 h)	30 min	119–4320 min (2.0–72 h)
IVH	Infarction and/or fibrin deposition	1380 min (23 h)	90 min	285–4050 min (4.8–67.5 h)
IVH	Plasma cell deciduitis	270 min (4.5 h)	30 min	90–3780 min (1.5–63 h)

^a AI is inclusive of acute chorioamnionitis, basal/decidual neutrophils, and acute inflammatory infiltrate in the abruption.^b This combination was not significant (n=3; p=0.23).^c This combination was significant (p=0.005); comparison between IVH cases with AI vs. IVH cases without AI.