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The frequency and clinical significance of intra-amniotic infection and/or inflammation in women with placenta previa and vaginal bleeding: an unexpected observation

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Abstract

Objective—Idiopathic vaginal bleeding, a common complication of pregnancy, increases the risk of SGA neonate, pre-eclampsia and preterm delivery and can be the only clinical manifestation of intra-amniotic infection and/or inflammation (IAI). Placenta previa is thought to be protective against ascending intrauterine infection, yet an excess of histologic chorioamnionitis has been reported in this condition. The aim of this study was to determine the frequency and clinical significance of IAI in women with placenta previa and vaginal bleeding in the absence of preterm labor.

Study design—A retrospective cohort study including 35 women with placenta previa and vaginal bleeding <37 weeks of gestation who underwent amniocentesis was undertaken. Patients with multiple gestations were excluded. Intra-amniotic infection was defined as a positive culture for microorganisms, and intra-amniotic inflammation as an elevated amniotic fluid interleukin (IL)-6 concentration. IL-6 concentrations were determined by ELISA in 28 amniotic fluid samples available. Non-parametric statistics were used for analysis.

Results—1) The prevalence of intra-amniotic infection was 5.7% (2/35), and that of IAI was 17.9% (5/28); 2) the gestational age at delivery was lower in patients with IAI than in those without IAI (29.4 weeks, IQR: 23.1–34.7 vs. 35.4 weeks, IQR: 33.9–36.9; p=0.028); and 3) patients with placenta previa and IAI had a higher rate of delivery within 48 hours (80% (4/5) vs. 19% (4/21); p=0.008) than those without IAI.

Conclusions—Patients with placenta previa presenting with vaginal bleeding have intra-amniotic infection in 5.7% of the cases, and intra-amniotic infection and/or inflammation in 17.9%. Intra-amniotic infection and/or inflammation in patients with placenta previa and vaginal bleeding is a risk factor for preterm delivery within 48 hours.

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Keywords

idiopathic vaginal bleeding; preterm labor; preterm delivery; prematurity; intra-amniotic inflammation; chorioamnionitis; deciduitis; cytokines; IL-6

INTRODUCTION

Placenta previa complicates 0.3 to 0.5% of pregnancies[1,2], and in approximately 70% of cases, women will experience at least one episode of vaginal bleeding during the second and third trimesters of pregnancy[2,3]. Contractions associated with cervical change can cause partial detachment of the placenta and it has been proposed that this is the mechanism whereby vaginal bleeding occurs in these cases[3]. However, patients with placenta previa can also present with an episode of vaginal bleeding in the absence of contractions.

Idiopathic vaginal bleeding is a common complication of pregnancy and has been associated with adverse pregnancy outcome [4] such as preeclampsia [5], small-for-gestational age (SGA) neonate [6–8] and preterm delivery [6–13]. Recently, idiopathic vaginal bleeding during pregnancy has been identified as the only clinical manifestation of intrauterine infection [11]. Traditionally, it has been believed that placenta previa may be protective against ascending intrauterine infection. Yet, pathologic studies have reported an excess of histologic chorioamnionitis in this condition [14]. A recent study demonstrated that a subset of patients with placenta previa and an episode of spontaneous preterm labor with intact membranes have evidence of intra-amniotic infection and/or inflammation (IAI) [14]. Thus, the aim of this study was to determine the frequency and clinical significance of IAI in women with placenta previa and vaginal bleeding in the absence of preterm labor.

MATERIALS AND METHODS

Study design and population

A retrospective cohort study was conducted by searching our clinical database and bank of biological samples and included patients admitted with the diagnosis of placenta previa and vaginal bleeding who met the following criteria: 1) singleton gestation; 2) diagnosis of placenta previa confirmed by ultrasound; 3) gestational age <37 weeks; and 4) amniocentesis performed. Patients with preterm labor, preterm prelabor rupture of membranes (PROM) and those with suspected placental abruption were excluded from the study.

Between January 1998 and July 2007, 168 patients with placenta previa and vaginal bleeding were admitted to the Sotero del Rio Hospital in Puente Alto, Santiago, Chile. Patients presenting with vaginal bleeding to this institution are offered amniocentesis as part of standard obstetrical practice because previous studies have suggested an association between vaginal bleeding, intra-amniotic infection and chorioamnionitis [11,15]. After counseling, 66 patients underwent amniocentesis, and after exclusion criteria were applied, 35 patients were left for analysis. All women provided written informed consent prior to the collection of amniotic fluid. The collection and utilization of amniotic fluid for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

Definitions

Placenta previa was defined as a placenta that overlies or is proximate to the internal cervical os based on trans-vaginal ultrasound [3]. Patients with low lying placenta at the

time of amniocentesis were not included in the study. Preterm labor was defined by the presence of regular uterine contractions occurring at a frequency of at least two every 10 minutes before 37 weeks of gestation. Vaginal bleeding was diagnosed by sterile speculum examination confirming the presence of blood coming through the external os of the cervix. Intra-amniotic infection was defined as a positive amniotic fluid culture for microorganisms. Intra-amniotic inflammation was diagnosed by an amniotic fluid interleukin (IL)-6 concentration ≥2.6ng/mL [16].

Sample collection

Amniotic fluid samples were obtained by trans-abdominal amniocentesis performed for evaluation of the microbial status of the amniotic cavity and/or assessment of fetal lung maturity. Amniotic fluid samples were transported to the laboratory in a sterile capped syringe and cultured for aerobic/anaerobic bacteria and genital mycoplasmas. White blood cell count, glucose concentration and Gram stain were also performed shortly after collection as previously described [17–19]. The results of these tests were used for clinical management. Amniotic fluid not required for clinical assessment was centrifuged for 10 minutes at 4°C and the supernatant was aliquoted and stored at −70°C. Amniotic fluid IL-6 concentrations were determined for research purposes in 28 patients whose amniotic fluid samples were available for analysis.

Statistical Analysis

The normality of the data was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since the data were not normally distributed, non-parametric tests were used for analyses. Comparisons between proportions were performed with Chi square test, and Mann-Whitney U test was used for analyses of continuous variables. A p-value of <0.05 was considered statistically significant. The statistical package used was SPSS v.15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics of the study population

Table I displays the demographic and clinical characteristics of patients included in the study. There was no significant difference in the median maternal age and pre-gestational body mass index, as well as in the proportion of nulliparity and history of previous preterm birth between patients with and without IAI. Among patients with placenta previa and vaginal bleeding, those with IAI had a lower gestational age at amniocentesis than those without IAI (Table I).

The prevalence and clinical significance of intra-amniotic infection and/or inflammation in patients with placenta previa and vaginal bleeding

Among patients with placenta previa and vaginal bleeding, the prevalence of intra-amniotic infection was 5.7% (2/35), and that of IAI was 17.9% (5/28). The microorganisms recovered from the amniotic cavity were *Escherichia coli* and *Streptococcus viridans*. The gestational age at delivery was significantly lower in patients with IAI than in those without IAI (29.4 weeks, IQR: 23.1–34.7 vs. 35.4 weeks, IQR: 33.9–36.9; p=0.028). Patients with placenta previa and vaginal bleeding <28 weeks of gestation had a higher rate of IAI than those admitted >28 weeks, although this difference was not statistically significant [30% (3/10) vs. 11.1% (2/18); p=0.2].

Clinical information at the time of delivery was available in 33 cases (two patients delivered elsewhere). Overall, the rate of delivery <34 weeks and <37 weeks was 42.4% (14/33) and 81.2% (27/33) respectively. Patients with placenta previa and vaginal bleeding, in the

presence of IAI, had a significantly higher rate of delivery within 48 hours [80% (4/5) vs. 19% (4/21); p=0.008), 7 days [80% (4/5) vs. 28.6% (6/21); p=0.03] and at <32 weeks of gestation [75% (3/4) vs. 8.3 % (1/12); p=0.008] than those without IAI. No differences were observed in the rate of delivery at <34 [80% (4/5) vs. 43.8% (7/16); p=0.2].

Four patients with IAI delivered within 48 hours and at ≤32 weeks. Three cases developed spontaneous preterm labor after admission and one case required an emergency cesarean section due to persistent bleeding. Interestingly, one case had an elevated amniotic fluid IL-6 concentration (3.9ng/mL) at 23.6 weeks but delivered at term. In addition, one of the patients with intra-amniotic infection (amniotic fluid culture positive for *Escherichia coli*) had normal amniotic fluid IL-6 concentration (0.26ng/mL) and delivered within 24 hours.

DISCUSSION

Principal findings of the study

Among patients with placenta previa and idiopathic vaginal bleeding, the prevalence of intra-amniotic infection was 5.7% and that of IAI 17.9%. Similar to pregnant women with normal placentation and IAI, patients with placenta previa and IAI are at increased risk for delivery within 48 hours, 7 days and at <32 weeks of gestation.

Intra-amniotic infection in the context of placenta previa

It has been proposed that microorganisms may gain access to the amniotic cavity through any of the following pathways: 1) ascending infection from the vagina and the cervix; 2) hematogenous dissemination through the placenta; 3) retrograde seeding from the peritoneal cavity through the fallopian tubes; and 4) accidental introduction at the time of invasive procedures (e.g. amniocentesis, chorionic villous sampling, shunting). The most common pathway of intrauterine infection is the ascending route[20]. In a cohort of 206 patients with spontaneous preterm labor and intact membranes, in the absence of placenta previa, the frequency of intra-amniotic infection was 10%, IAI was found in 32% of cases and 53% of the placentas available for analysis had histologic chorioamnionitis[16]. Interestingly, a recent study from the same group of investigators[14] in patients with spontaneous preterm labor and intact membranes in cases of placenta previa reported a rate of 4.9%, 16.7% and 19% for intra-amniotic infection, IAI and histologic chorioamnionitis, respectively. Among patients with histologic chorioamnionitis, inflammation of the choriodecidua (exposed to the cervical canal) was present in all cases (8/8), but inflammation of the chorionic plate existed in 63% (5/8) of them[14]. It is possible that placenta previa may act as a mechanical barrier preventing, at least partially, ascending intra-amniotic infection[14].

Idiopathic vaginal bleeding is associated with intra-amniotic infection in 14% of patients[11]. The finding that 5.7% of patients with placenta previa and vaginal bleeding have intra-amniotic infection suggest that vaginal bleeding may be also a manifestation of microbial invasion in a subset of patients with placenta previa. The microorganisms recovered from the amniotic cavity in the two patients in this study were *Escherichia coli* and *Streptococcus viridans*. These bacteria have been previously reported in cervical and vaginal flora of pregnant women[21–23] suggesting that, even in the presence of placenta previa, ascending infection is still a plausible mechanism for microorganisms to gain access to the amniotic cavity. Thus, the traditional view that vaginal bleeding in patients with placenta previa is likely to be due to the presence of the placenta previa itself and not of IAI, needs to be reconsidered. Exclusion of intra-amniotic infection and/or inflammation should be considered as part of the clinical evaluation of women with placenta previa presenting with vaginal bleeding, because those patients are at increased risk for adverse pregnancy

outcomes. Further studies are required to determine the prevalence and significance of intra-amniotic infection using molecular microbiologic techniques in these patients.

The clinical significance of vaginal bleeding in patients with placenta previa

Bleeding of unknown etiology in the second half of pregnancy has been associated with adverse pregnancy outcome including preterm delivery[6–13], preterm PROM[8,11,24], preeclampsia[5], SGA[6–8], stillbirths[7,12], fetal anomalies[6,7,9,10,12], as well as admission to neonatal intensive care unit, reduced birth weight and low Apgar scores[8,13].

This study further demonstrates that, among patients with placenta previa and idiopathic vaginal bleeding, the gestational age at delivery was significantly lower in those with IAI compared to those without IAI, as well as a significantly higher rate of delivery within 48 hours, 7 days and at <32 weeks. The amniocentesis-to-delivery interval was not significantly different between the two groups (data not shown). This may be explained due to the following: 1) one patient with an elevated amniotic fluid IL-6 concentration at 23.6 weeks of gestation delivered at term (37.3 weeks); and 2) since patients with placenta previa are delivered at approximately 36–37 weeks of gestation[3], and the median gestational age at amniocentesis in patients without IAI was 31.1 weeks, the amniocentesis-to-delivery interval for this group was similar to the IAI group.

It can be postulated that ascending infection may cause a localized inflammatory response in the decidua (deciduitis) that can present clinically as vaginal bleeding[11,25,26]. In response to bacterial products, the decidua can produce IL-1β [27] and tumor necrosis factor (TNF)-α[28] which, in turn, can stimulate prostaglandin production by amnion, decidua, and myometrium[27–30]. Prostaglandins are considered the key mediators for the onset of labor by induction of myometrial contractility[31–35] and changes in the extracellular matrix metabolism associated with cervical ripening[36–40]. In addition, IL-1β and TNF-α can stimulate the production of tissue factor[41,42] and generation of thrombin[42]. It has been demonstrated that thrombin stimulates myometrial contractility in a dose dependent manner[43–46] and that thrombin-antithrombin complexes, a marker of *in vivo* generation of thrombin, are increased in the plasma[47] and amniotic fluid[48] of women in preterm labor.

In conclusion, 17.9% of patients with placenta previa presenting with idiopathic vaginal bleeding have intra-amniotic infection and/or inflammation, which is a risk factor for preterm delivery within 48 hours, 7 days and <32 weeks of gestation. These findings are novel and suggest that vaginal bleeding may be a symptom of subclinical intra-amniotic infection and/or inflammation in patients with placenta previa.

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Table I

Demographic and clinical characteristics of patients with and without IAI

	With IAI (n=5)	Without IAI (n=23)	P value
Maternal age (years)	32 (27.5–38.0)	32 (28.0–35.8)	0.9
Pregestational BMI (kg/m^2)	23.2 (20.5–28.3)	24.8 (22.3–29.0)	0.5
Smoking (%)	0 (0/5)	4.3 (1/23)	0.6
Nulliparous (%)	0 (0/5)	21.7 (5/23)	0.3
Previous preterm delivery (%)	0 (0/5)	21.7 (5/23)	0.3
Gestational age at amniocentesis (weeks)	23.6 (23.0–30.7)	31.1 (28.1–33.9)	0.03
Gestational age at delivery (weeks)	29.4 (23.1–34.7)	35.4 (33.9–36.9)	0.03
Birth weight (grams)	1,570 (545–2,620)	2,410 (1,970–2,913)	0.06
Amniotic fluid WBC count (cells/mm^3)	5 (1–430)	2 (0–5)	0.2
IL-6 (ng/mL)	58.5 (2.1–145.5)	0.9 (0.5–1.3)	0.03

Results are expressed as median (interquartile range) or percentage (proportion)

BMI: body mass index; IL-6: interleukin-6