J. Perinat. Med. 38 (2010) 45–53 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/JPM.2009.133

The prognosis of pregnancy conceived despite the presence of an intrauterine device (IUD)

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Abstract

Objective: Intrauterine devices (IUDs) are used for contraception worldwide; however, the management of pregnancies with an IUD poses a clinical challenge. The purpose of this study was to determine the outcome of pregnancy in patients with an IUD.

Study design: A retrospective cohort study (December 1997–June 2007) was conducted. The cohort consisted of 12,297 pregnancies, of which 196 had an IUD. Only singleton pregnancies were included. Logistic regression analysis was used to adjust for potential confounders between the groups.

Results: 1) Pregnancies with an IUD were associated with a higher rate of late miscarriage, preterm delivery, vaginal bleeding, clinical chorioamnionitis, and placental abruption than those without an IUD; 2) among patients with available histologic examination of the placenta, the rate of histologic chorioamnionitis and/or funisitis was higher in patients with an IUD than in those without an IUD (54.2% vs. 14.7%; $P < 0.001$). Similarly, among patients who underwent an amniocentesis, the prevalence of microbial invasion of the amniotic cavity (MIAC) was also higher in pregnant women with an IUD than in those without an IUD (45.9% vs. 8.8%; $P < 0.001$); and 3) intra-amniotic infection caused by *Candida* species was more frequently present in pregnancies with an IUD than in those without an IUD (31.1% vs. 6.3%; $P < 0.001$).

Conclusion: Pregnant women with an IUD are at a very high risk for adverse pregnancy outcomes. This finding can be attributed, at least in part, to the high prevalence of intra-amniotic infection and placental inflammatory lesions observed in pregnancies with an IUD.

Keywords: Chorioamnionitis; intrauterine device; microbial invasion of the amniotic cavity; pregnancy; prematurity; preterm delivery; preterm labor; preterm prelabor rupture of the membranes.

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Introduction

Intrauterine devices (IUDs) are used for contraception worldwide. Despite the presence of an IUD, the failure rate of this contraceptive method ranges from 0.3 to 2.3% [12, 39, 40, 51]. Compelling evidence has demonstrated that pregnancies with an IUD are associated with an increased risk of spontaneous abortion and preterm delivery due to infection [2, 52], and the risk of maternal septic complications also increases in such cases [18]. It has been reported that the miscarriage rate is reduced if the IUD is removed in early pregnancy [18, 48, 52], and it is recommended that the IUD should be removed during the first trimester of pregnancy [17]. However, if the IUD remains in the uterine cavity during pregnancy, the management of such pregnancies poses a clinical challenge. There is a paucity of data about the prevalence and clinical significance of intra-amniotic infection and placental inflammation associated with pregnancies with a retained IUD. The purpose of this study was to determine the outcomes of pregnancy in patients with an IUD in a large unselected population.

Patients and methods

Study design and population

A retrospective cohort study was conducted including women who delivered at the Sótero del Rio Hospital (Santiago, Chile) from December 1997 to June 2007. This cohort consisted of 12,297 pregnancies, of which 196 had a Copper T 380A IUD *in situ* during pregnancy. Only singleton pregnancies and parous women were

included. Patients post-IUD removal during early pregnancy (n = 12) were excluded. All patients provided written informed consent at the time of enrolment. The Institutional Review Boards of both the Sótero del Rio Hospital and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health (NICHD/NIH/DHHS) approved the collection of biologic materials and data from these patients for research purposes.

Clinical definitions

Preterm birth was defined as delivery occurring before 37 completed weeks of gestation. Spontaneous preterm labor (PTL) was defined by the presence of regular uterine contractions occurring at a frequency of at least two every 10 min associated with cervical changes before 37 completed weeks of gestation that required hospitalization [25]. The diagnosis of preterm prelabor rupture of the membranes (preterm PROM) was confirmed by pooling of amniotic fluid in the vagina in association with positive nitrazine and ferning tests or by a positive amniocentesis-dye test before 37 completed weeks of gestation. Indicated preterm birth was defined as delivery of a preterm neonate because of medical or obstetrical complications that threatened maternal or fetal condition. Preeclampsia was defined as the presence of hypertension (systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg on at least two occasions, 4 h–1 week apart), occurring after 20 weeks of gestation in a woman with previously normal blood pressure, and proteinuria ($\geq$300 mg in a 24-h urine collection or one dipstick measurement $\geq$1+) [1]. A small for gestational age (SGA) neonate was defined as birth weight below the 10th percentile for gestational age [23]. Clinical chorioamnionitis was diagnosed in the presence of fever ($\geq$37.8°C) and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal tachycardia ($\geq$100 beats/min), maternal leukocytosis ($\geq$15,000 cells/mm^3), and fetal tachycardia ($\geq$160 beats/min) [19]. Placental abruption was identified based on a clinical diagnosis which included the following criteria: 1) painful vaginal bleeding; 2) uterine tenderness or hypertonicity; and 3) retroplacental hematoma on the placental surface or on the basis of prenatal sonographic diagnosis [59]. Spontaneous abortion was defined as spontaneous pregnancy termination prior to 20 weeks of gestation.

Composite neonatal morbidity was defined as the presence of any following conditions: neonatal sepsis or suspected sepsis, respiratory distress syndrome, patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, or necrotizing enterocolitis. Neonatal sepsis was diagnosed in the presence of a positive blood culture. Suspected neonatal sepsis was diagnosed in the absence of a positive blood culture when two or more of the following criteria were present: 1) white blood cell (WBC) count of $<$5000 cells/mm^3; 2) polymorphonuclear leukocyte count of $<$1800 cells/mm^3; and 3) ratio of immature neutrophils to total neutrophils $>$0.2 [21]. The diagnosis of respiratory distress syndrome required the presence of respiratory grunting and retracting, increased need for oxygen, and diagnostic radiographic and laboratory findings in the absence of evidence for other causes of respiratory disease [21]. Patent ductus arteriosus was diagnosed by the presence of clinical signs and symptoms (heart murmur, increased pulse pressure, decreased mean arterial blood pressure, and bounding peripheral pulses) and confirmed by an echocardiogram demonstrating blood flow (left to right or bi-directional) through the patent ductus arteriosus [58]. Bronchopulmonary dysplasia was diagnosed if the neonate required oxygen and ventilatory therapy for $>$28 days during the first 2 months of life, had typical radiographic changes and/or had dysplasia of the bronchopulmonary tree at autopsy [29]. Intraventricular hemorrhage was diagnosed by ultrasonographic examination of the neonatal head. Necrotizing enterocolitis was diagnosed in the presence of abdominal distention and feeding intolerance for at least 24 h (vomiting or increased gastric residual) with clear radiologic evidence of intramural air, perforation, meconium plug syndrome, or definite surgical or autopsy findings of necrotizing enterocolitis [21].

Amniotic fluid sample collection

Amniocentesis was performed at the discretion of the treating physician. Amniotic fluid samples were obtained by transabdominal amniocentesis or at the time of cesarean delivery. All specimens were cultured for the presence of microorganisms including aerobic and anaerobic bacteria as well as genital *Mycoplasmas*. WBC count, glucose concentration, and Gram stain were also performed shortly after collection as previously described [41–43]. Intra-amniotic infection was defined as a positive amniotic fluid culture for microorganisms. Intra-amniotic inflammation was diagnosed by an amniotic fluid WBC count $>$50 cells/mm^3 [43].

Histopathologic examination of the placenta

Pathologic examination of the placenta was performed systematically based on the diagnostic criteria previously described [38]. The maternal inflammatory response (histologic chorioamnionitis) was described in detail as follows: 1) acute subchorionitis/chorionitis (stage 1 early); 2) acute chorioamnionitis (stage 2 intermediate); 3) necrotizing chorioamnionitis (stage 3 late); 4) subacute chorioamnionitis (stage 3 late); and 5) subchorionic microabscess (severe). The fetal inflammatory response (funisitis) was also classified as follows by inflammation in the umbilical cord: 1) umbilical phlebitis/chorionic vasculitis (stage 1 early); 2) umbilical arteritis (stage 2 intermediate); 3) necrotizing funisitis (stage 3 late); and 4) intense chorionic vasculitis with recent non-occlusive chorionic vessel thrombi (severe).

Statistical analysis

The normality of the data was tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. Since the data were normally distributed, mean and standard deviation were reported for continuous variables, and the number and percentage were presented for categorical variables. Differences in the continuous variables between the two groups were estimated using Student *t*-test. Comparisons of proportions were performed by χ^2 or Fisher's exact tests. Associations between the presence of IUD in pregnancy and the obstetrical outcomes were analyzed by means of logistic regression models with adjustment for confounding factors: maternal age, parity, history of preterm birth, gestational age at delivery, underlying medical condition, smoking status, and pre-pregnancy body mass index (BMI). A $P<0.05$ was considered statistically significant. The statistical analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago, IL, USA).

Results

Demographic characteristics and obstetrical outcomes of the study population

Table 1 presents the demographic characteristics and obstetrical outcomes of the study population. Pregnancies with an IUD had a significantly lower mean gestational age at delivery than those without an IUD ($P<0.001$), and were asso-

ciated with a higher rate of spontaneous PTL, preterm PROM, and late spontaneous abortion (>12 weeks of gestation). These results remained significant after adjustment for maternal age, parity, history of preterm birth, underlying medical condition, smoking status, and pre-pregnancy BMI. Moreover, pregnancies with an IUD were associated with a higher rate of vaginal bleeding, clinical chorioamnionitis, and placental abruption than those without an IUD. These results remained significant after adjustment for maternal age, parity, gestational age at delivery, underlying medical condition, smoking status, and pre-pregnancy BMI.

Amniotic fluid analysis

Amniocenteses were performed on 2081 patients from the study population. The indications and laboratory results of amniotic fluid analysis are shown in Table 2. Patients with an IUD more frequently underwent amniocentesis for the detection of microbial invasion of the amniotic cavity (MIAC) than those without an IUD (94.9% vs. 66.8%; $P<0.001$). The mean gestational age at amniocentesis was earlier in patients with an IUD than in those without an IUD (26.1±6 weeks vs. 32.6±6 weeks; $P<0.001$). Overall, the prevalence of a positive amniotic fluid culture was higher in patients with an IUD than in those without an IUD (45.9% vs. 8.8%; $P<0.001$). After adjustment for gestational age at amniocentesis, logistic regression analysis showed that the presence of IUD in pregnancy was an independent explanatory variable for the occurrence of MIAC; the adjusted odds ratio (OR) was 4.9 [95% confidence interval (CI), 3.1–7.8]. Table 3 displays the amniotic fluid analysis of patients with spontaneous PTL with intact membranes and that of those with preterm PROM according to the presence or absence of IUD in pregnancy. The prevalence of a positive amniotic fluid culture was higher in patients with an IUD than in those without an IUD among both cases of spontaneous PTL with intact membranes (38.5% vs. 5.2%; $P<0.001$) and preterm PROM (57.1% vs. 27.0%; $P<0.001$). Table 4 displays the microorganisms isolated from the amniotic fluid. *Ureaplasma urealyticum* was the most frequent microorganism isolated from the amniotic cavity of patients both with (48.9%) and without (48.9%) an IUD. *Candida* species was the second common microorganism isolated from the amniotic fluid of patients with an IUD, and significantly more frequent in patients with an IUD than in those without an IUD (31.1% vs. 6.3%; $P<0.001$).

Placental histology

Placental histopathologic examinations were available for 43.4% (5340/12,297) of the study population (pregnancies with an IUD, 54.6% [107/196]; those without an IUD, 43.2% [5233/12,101]). The diagnosis of chorioamnionitis was stratified based on the presence of either a maternal and/or fetal

Table 1 Demographic characteristics and obstetrical outcomes of the study population.

Variable	No IUD (n=12,101)	Pregnancy with an IUD (n=196)	Crude OR (95% CI)	Adjusted OR (95% CI)
Characteristics				
Age (years)	29.6±6.5	29.5±7.3	1.0 (0.9–1.0)	
Parity	1.8±1.2	1.9±1.0	1.0 (0.9–1.1)	
Gestational age at delivery (weeks)	37.5±5.1	28.5±8.6	0.8 (0.8–0.9)	
History of preterm birth	1683 (13.9)	24 (12.2)	0.9 (0.6–1.3)	
Underlying medical condition	1273 (10.5)	16 (8.2)	0.8 (0.5–1.3)	
Smoking	1609 (13.4)	17 (8.8)	0.6 (0.4–1.1)	
Pre-pregnancy BMI (kg/m^2)	26.0±5.1	26.9±5.0	1.0 (0.9–1.0)	
Obstetrical outcomes				
Preterm birth	2503 (20.7)	110 (56.1)	4.9 (3.7–6.5)	5.8 (4.3–8.0)*
Spontaneous preterm labor	946 (7.8)	34 (17.3)	2.5 (1.7–3.6)	2.5 (1.7–3.8)*
Preterm PROM	714 (5.9)	68 (34.7)	8.5 (6.3–11.5)	9.4 (6.8–13.0)*
Indicated preterm birth	843 (7.0)	8 (4.1)	0.6 (0.3–1.2)	0.7 (0.3–1.4)*
Late spontaneous abortion (>12 weeks)	146 (1.2)	31 (15.8)	15.4 (10.1–23.3)	16.8 (10.6–26.7)*
Fetal death	188 (1.6)	9 (4.6)	3.0 (1.5–6.0)	1.5 (0.7–3.2)**
Preeclampsia	557 (4.6)	4 (2.0)	0.4 (0.2–1.2)	0.6 (0.2–1.6)**
SGA	1141 (9.4)	10 (5.1)	0.5 (0.3–1.0)	0.7 (0.4–1.4)**
Vaginal bleeding	657 (5.4)	37 (18.9)	4.1 (2.8–5.8)	3.1 (2.1–4.7)**
Clinical chorioamnionitis	209 (1.7)	16 (8.2)	5.1 (3.0–8.6)	4.1 (2.3–7.2)**
Placental abruption	249 (2.1)	16 (8.2)	4.2 (2.5–7.2)	3.4 (2.0–5.9)**
Placenta previa	186 (1.5)	4 (2.0)	1.3 (0.5–3.6)	0.7 (0.2–2.9)**
Cesarean delivery	3765 (31.1)	61 (31.1)	1.0 (0.7–1.4)	1.4 (0.9–2.1)**
Fetal congenital malformation	828 (6.8)	15 (7.7)	1.1 (0.6–1.9)	1.4 (0.8–2.4)**

Data are expressed as number (percentage) or mean±SD.

OR=odds ratio, CI=confidence interval, IUD=intrauterine device, BMI=body mass index, PROM=prelabor rupture of the membranes, SGA=small for gestational age.

*Adjusted for age, parity, history of preterm birth, underlying medical condition, smoking, and pre-pregnancy BMI.

**Adjusted for age, parity, gestational age at delivery, underlying medical condition, smoking, and pre-pregnancy BMI.

Table 2 Indications and laboratory results of amniotic fluid analysis according to the presence or absence of intrauterine device in pregnancy.

Variable	No IUD (n = 1983)	Pregnancy with an IUD (n = 98)	P-value
Indication			
Detection of MIAC	1324 (66.8)	93 (94.9)	<0.001
Evaluation of fetal lung maturity	194 (9.8)	3 (3.1)	0.021
Karyotyping	53 (2.7)	0 (0)	NS
Treatment of polyhydramnios	4 (0.2)	0 (0)	NS
Rh isoimmunization	37 (1.9)	0 (0)	NS
Obtained at cesarean delivery	371 (18.7)	2 (2.0)	<0.001
Laboratory result			
WBC count >50 cells/mm^3	235 (11.9)	44 (44.9)	<0.001
Glucose concentration <14 mg/dL	709 (35.8)	59 (60.2)	<0.001
Positive Gram stain	63 (3.2)	11 (11.2)	<0.001
Positive culture for microorganism	174 (8.8)	45 (45.9)	<0.001
Intra-amniotic infection/inflammation	309 (15.6)	59 (60.2)	<0.001

Data are expressed as number (percentage).
IUD = intrauterine device, MIAC = microbial invasion of the amniotic cavity, WBC = white blood cell, NS = not significant.

Table 3 Amniotic fluid analysis among cases with spontaneous PTL and preterm PROM according to the presence or absence of intrauterine device in pregnancy.

Laboratory result	No IUD	Pregnancy with an IUD	P-value
Spontaneous PTL with intact membranes	n = 762	n = 26	
WBC >50 cells/mm^3	47 (6.2)	7 (26.9)	<0.001
Glucose concentration <14 mg/dL	168 (22.0)	15 (57.7)	<0.001
Positive Gram stain	23 (3.0)	3 (11.5)	NS
Positive culture for microorganism	40 (5.2)	10 (38.5)	<0.001
Intra-amniotic infection/inflammation	68 (8.9)	11 (42.3)	<0.001
Preterm PROM	n = 348	n = 49	
WBC >50 cells/mm^3	124 (35.6)	32 (65.3)	<0.001
Glucose concentration <14 mg/dL	131 (37.6)	33 (67.3)	<0.001
Positive Gram stain	28 (8.0)	5 (10.2)	NS
Positive culture for microorganism	94 (27.0)	28 (57.1)	<0.001
Intra-amniotic infection/inflammation	156 (44.8)	38 (77.6)	<0.001

Data are expressed as number (percentage).
PTL = preterm labor, PROM = prelabor rupture of the membranes, IUD = intrauterine device, WBC = white blood cell, NS = not significant.

inflammatory response. The rate of histologic chorioamnionitis and/or funisitis was higher in patients with an IUD than in those without an IUD (Table 5). Histologic chorioamnionitis was more common in patients with an IUD compared to those without an IUD (Table 5); and the rates of acute chorioamnionitis, necrotizing chorioamnionitis, and subacute chorioamnionitis were higher in patients with an IUD than in those without an IUD (Table 5). Similarly, funisitis was more common in patients with an IUD compared to those without an IUD (Table 5); and the rates of umbilical phlebitis/chorionic vasculitis, umbilical arteritis, and necrotizing funisitis were higher in patients with an IUD than in those without an IUD (Table 5). After adjustment for gestational age at delivery, logistic regression analysis showed that the presence of an IUD in pregnancy was an independent explanatory variable for the occurrence of histologic chorioamnionitis and/or funisitis; the adjusted OR was 3.4 (95% CI, 2.2–5.3). In cases of placental abruption, placental histologic examinations were available for 115 patients; the rate of histologic chorioamnionitis and/or funisitis was higher in cases of placental abruption with an IUD than in those without an IUD (76.9% [10/13] vs. 14.7% [15/102], P < 0.001).

Neonatal outcomes

Neonates born to mothers with an IUD had a lower mean birth weight (P < 0.001) and a higher rate of Apgar score of <7 at 5 min (P < 0.001) than those of mothers without an IUD. In addition, a significantly higher proportion of neonates born to mothers with an IUD had neonatal sepsis or suspected sepsis, respiratory distress syndrome, patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death than those born to mothers without an IUD (Table 6). How-

Table 4 Culture isolates from amniotic fluid according to the presence or absence of intrauterine device in pregnancy.

Species	No IUD (n = 174)	Pregnancy with an IUD (n = 45)	P-value
Ureaplasma urealyticum	85 (48.9)	22 (48.9)	NS
Candida species	11 (6.3)	14 (31.1)	<0.001
Staphylococcus coagulase (–)	14 (8.0)	6 (13.3)	NS
Mycoplasma hominis	19 (10.9)	5 (11.1)	NS
Staphylococcus coagulase (+)	4 (2.3)	2 (4.4)	NS
Streptococcus viridans	4 (2.3)	1 (2.2)	NS
Streptococcus pneumoniae	3 (1.7)	1 (2.2)	NS
Enterococcus species	10 (5.7)	1 (2.2)	NS
Peptostreptococcus	3 (1.7)	1 (2.2)	NS
Others	55 (31.6)	0 (0)	<0.001

Data are expressed as number (percentage).
IUD = intrauterine device, NS = not significant.

ever, the presence of an IUD in pregnancy was not an independent explanatory variable for composite neonatal morbidity after adjustment for gestational age at delivery; the adjusted OR was 0.7 (95% CI, 0.5–1.2). Of interest, among cases with term delivery and no evidence of histologic chorioamnionitis and/or funisitis, the prevalence of neonatal sepsis or suspected sepsis was higher in neonates born to mothers with an IUD than in those without IUD (7.7% [2/26] vs. 1.2% [42/3544], P = 0.04).

Discussion

Principal findings of this study

Pregnancies with an IUD: 1) had a higher rate of MIAC and histologic chorioamnionitis; 2) had a higher rate of intra-amniotic infection caused by *Candida* species; 3) were associated with a higher rate of late miscarriage, preterm delivery, vaginal bleeding, clinical chorioamnionitis, and placental abruption; and 4) had poorer neonatal outcomes in comparison to pregnancies without an IUD.

Pregnancy with an IUD, intra-amniotic infection, and microbial biofilms

We report for the first time the placental histologic evaluation of pregnancies with an IUD in a cohort study using standardized criteria for placental findings consistent with intra-amniotic infection. Among patients with available placental histologic evaluation, the rate of histologic chorioamnionitis was higher in patients with an IUD than in those without an IUD. Moreover, among the lesions for both maternal and fetal responses of chorioamnionitis, severe inflammatory lesions, such as necrotizing chorioamnionitis and umbilical arteritis were observed more frequently in patients with an IUD than in those without an IUD. Similarly, amniotic fluid analyses among both cases of spontaneous PTL with intact membranes and preterm PROM showed a higher prevalence of intra-amniotic infection/inflammation in patients with an

Table 5 Histologic analysis of the placenta according to the presence or absence of intrauterine device in pregnancy.

Histologic finding	No IUD (n = 5233)	Pregnancy with an IUD (n = 107)	P-value
Histologic chorioamnionitis, maternal response			
Any	672 (12.8)	56 (52.3)	<0.001
Stage 1 early: acute subchorionitis/chorionitis	446 (8.5)	5 (4.7)	NS
Stage 2 intermediate: acute chorioamnionitis	157 (3.0)	14 (13.1)	<0.001
Stage 3 late: necrotizing chorioamnionitis	48 (0.9)	22 (20.6)	<0.001
Stage 3 late: subacute chorioamnionitis	16 (0.3)	14 (13.1)	<0.001
Severe: subchorionic microabscess	5 (0.1)	1 (0.9)	NS
Funisitis, fetal response			
Any	440 (8.4)	47 (43.9)	<0.001
Stage 1 early: umbilical phlebitis/chorionic vasculitis	319 (6.1)	18 (16.8)	<0.001
Stage 2 intermediate: umbilical arteritis	96 (1.8)	20 (18.7)	<0.001
Stage 3 late: necrotizing funisitis	22 (0.4)	8 (7.5)	<0.001
Severe: intense chorionic vasculitis with recent non-occlusive chorionic vessel thrombi	3 (0.1)	1 (0.9)	NS
Histologic chorioamnionitis and/or funisitis	770 (14.7)	58 (54.2)	<0.001

Data are expressed as number (percentage).
IUD = intrauterine device, NS = not significant.

Table 6 Neonatal outcomes according to the presence or absence of intrauterine device in pregnancy.

Neonatal outcome	No IUD (n = 11,632)	Pregnancy with an IUD (n = 151)	P-value
Birth weight (g)	3208 ± 1012	2211 ± 1133	<0.001
Apgar score <7 at 5 min	248 (2.1)	20 (13.2)	<0.001
NICU admission	1524 (13.1)	64 (42.4)	<0.001
Neonatal sepsis or suspected sepsis	686 (5.9)	36 (23.8)	<0.001
Respiratory distress syndrome	256 (2.2)	18 (11.9)	<0.001
Patent ductus arteriosus	188 (1.6)	8 (5.3)	0.002
Bronchopulmonary dysplasia	91 (0.8)	11 (7.3)	<0.001
Intraventricular hemorrhage	97 (0.8)	10 (6.6)	<0.001
Necrotizing enterocolitis	49 (0.4)	5 (3.3)	<0.001
Composite neonatal morbidity*	923 (7.9)	55 (36.4)	<0.001
Neonatal death	174 (1.5)	16 (10.6)	<0.001

Data are expressed as number (percentage) or mean ± SD.
IUD = intrauterine device, NICU = neonatal intensive care unit.
*Defined as the presence of any of the following conditions: neonatal sepsis or suspected sepsis, respiratory distress syndrome, patent ductus arteriosus, bronchopulmonary dysplasia, intraventricular hemorrhage, or necrotizing enterocolitis.

IUD compared to those without an IUD. Previous studies have demonstrated the formation of biofilms on the IUD surface [6, 9, 35, 37]. Biofilms are defined as structured communities of microorganisms characterized by cells that are attached to a living or inert surface [15]. Bacterial biofilms have been implicated in several infectious diseases, such as periodontitis, otitis media, endocarditis, prostatitis, biliary tract infections, and many others associated with a medical device [10]. It has been previously reported that bacteria can develop a biofilm in the amniotic cavity and that such a biofilm has been found in a case with amniotic fluid ''sludge'' [44]. Indeed, the presence of amniotic fluid ''sludge'' is an independent risk factor for MIAC, histologic chorioamnionits, and spontaneous preterm delivery in patients with PTL and intact membranes as well as asymptomatic patients with a short cervix [16, 31]. Since IUDs are in the uterine cavity, not inside the amniotic cavity, future studies are warranted to determine the prevalence of amniotic fluid ''sludge'' and the presence of microbial biofilms in the amniotic fluid of pregnant women with an IUD.

Pregnancy with an IUD and *Candida* infection

Ureaplasma urealyticum and *Mycoplasma hominis* are the most common microorganism in intra-amniotic infection [45], which is consistent with the findings reported herein. In addition, this study reported a higher rate of intra-amniotic infection caused by *Candida* species in pregnancies with an IUD than in those without an IUD. These findings are in agreement with previous reports demonstrating an association between intra-amniotic *Candida* infection and pregnancies with an IUD [8, 14, 28, 33, 46, 47, 50, 57]. *Candida* species are common saprophytes in the genital tract and are present in up to 20–25% of pregnant women [55]. Despite the frequent prevalence of vaginal *Candida* infection during pregnancy, intra-amnioitc infection caused by *Candida* species is rare. Previous studies suggested two mechanisms by which *Candida* species could gain access to the amniotic cavity in pregnancies with an IUD: 1) endometrial yeast contamination may be present at the time of IUD insertion [47]; and 2) the strings of an IUD may serve as a route for ascending infection [13]. Chassot et al. [9] have demonstrated the *in vitro* adhesive capacity to IUDs of *Candida albicans* isolated from vaginal exudates of patients with vaginal candidiasis, and its formation of a biofilm which makes a progressive source of infection. Because of the higher prevalence of intra-amniotic *Candida* infection in pregnancies with an IUD, an accurate diagnosis and treatment should be considered.

Retained IUD and adverse pregnancy outcome

Several studies have reported a higher rate of miscarriage in women who conceive an intrauterine pregnancy despite the presence of an IUD [18, 48, 52]. Moreover, the present study showed a higher rate of fetal death. However, there was no significant association between the rate of fetal death and the presence of an IUD after adjustment for confounding factors, such as maternal age, parity, gestational age at delivery, underlying medical condition, smoking, and pre-pregnancy BMI.

The results of this study support an association between the presence of an IUD in pregnancy and preterm birth [7, 52]. Epidemiologic studies of preterm birth reveal that 40–45% of preterm births follow spontaneous PTL with intact membranes, 25–30% follow preterm PROM, and 30–35% are delivery for maternal or fetal indications [20, 49], which is consistent with findings of the present study. However, in pregnancies with an IUD, preterm PROM was the most common cause of preterm birth. The ultimate cause of membrane rupture in many cases of preterm PROM is unknown, but asymptomatic intrauterine infection is considered as a frequent precursor [20]. Of interest, pregnancies with an IUD were independently associated with preterm birth and preterm PROM even after adjustment for histologic chorioamnionitis and/or funisitis (data not shown).

Idiopathic vaginal bleeding during pregnancy has been proposed as one of the clinical manifestations of intrauterine infection [22]. Vaisbuch et al. [54] suggested that the total hemoglobin concentration in amniotic fluid is increased in intra-amniotic infection/inflammation. In the present study, pregnancies with an IUD were associated with a higher rate of vaginal bleeding. Thus, our findings are concordant with previous studies reporting that MIAC is associated with vaginal bleeding that may lead to subsequent preterm PROM and early preterm delivery [22, 54]. Moreover, patients with an IUD had a higher rate of clinical chorioamnionitis than patients without an IUD. This is consistent with the findings that the rates of histologic chorioamnionitis and MIAC were higher in patients with an IUD than in those without an IUD.

We have also demonstrated that pregnancies with an IUD were associated with a higher prevalence of placental abruption than pregnant women without an IUD. Although the primary etiology of placental abruption remains elusive, epidemiologic studies have identified an increased incidence of placental abruption in patients with a history of placental abruption, advanced maternal age, smoking, cocaine use, poor nutrition or socioeconomic status, multiparity, hypertensive disorders, chorioamnionitis, and preterm PROM [4, 5, 11, 27, 30, 36, 53, 56]. A previous study linked a chronic inflammatory process of placenta to placental abruption [3]. Indeed, an increased risk of placental abruption is associated with acute and chronic inflammatory processes that activate cytokines such as interleukin-1β and tumor necrosis factor-α [3]. Nath et al. [34] have demonstrated that histologic chorioamnionitis is associated with placental abruption. Moreover, neutrophil infiltration of the fetal membranes has been implicated in the association between preterm PROM and placental abruption, suggesting that the enhanced protease activity and expression by inflammatory cytokines in preterm PROM is involved in placental abruption [26, 34]. In this study, the rate of histologic chorioamnionitis and/or funisitis was higher in cases of placental abruption with an IUD than in those without an IUD. Thus, our findings support the hypothesis that an inflammatory state may contribute to the risk for placental abruption, preterm PROM, and spontaneous PTL with intact membranes.

A significantly higher proportion of neonates born to mothers with an IUD was admitted to neonatal intensive care unit (NICU) and had severe neonatal morbidity than that of those without an IUD. As expected, the most important factor associated with adverse neonatal outcomes was gestational age at delivery. However, among cases with term delivery and no evidence of histologic chorioamnionitis and/or funisitis, the prevalence of neonatal sepsis or suspected sepsis was higher in neonates born to mothers with an IUD than that of those without IUD. The susceptibility of term neonates born to mothers with an IUD to neonatal sepsis or suspected sepsis can be attributed to other pathogenesis in addition to gestational age at delivery and intrauterine inflammation. In accordance with previous studies [24, 32], the risk of congenital malformation was not increased in neonates born to mothers with an IUD compared to those without an IUD.

Several studies have established a higher risk of complications, such as miscarriage and sepsis, in pregnancies with a retained IUD than in those with early IUD removal [2, 18, 48, 52]. For this reason, the US Food and Drug Administration (FDA) recommends that IUDs whose tails are visible be removed in early pregnancy [17]. In our population there was no difference in obstetrical complications between pregnancies with a retained IUD and those with early IUD removal (data not shown). It is possible that the small sample size of cases following IUD removal during early pregnancy (n = 12) may account for these results, and larger study is needed to answer this research question.

In conclusion, this study provides evidence that pregnancies with a retained IUD are at increased risk for adverse pregnancy outcomes. This finding can be attributed, at least in part, to the higher rate of intraamniotic infection and placental inflammatory lesions observed in pregnancies with an IUD than in those without an IUD.

Acknowledgements

This research was supported (in part) by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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The authors stated that there are no conflicts of interest regarding the publication of this article.

Received May 4, 2009. Accepted June 22, 2009. Previously published online August 4, 2009.