Original research article

# Perinatal outcomes including long-term neuropsychiatric hospitalizations of offspring conceived during intrauterine contraceptive device use ☆

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**ABSTRACT**

*Objective:* To investigate short-term adverse perinatal outcomes and long-term neuropsychiatric hospitalizations through 18 years of age in offspring conceived during copper intrauterine device (IUD) use.
*Study design:* We conducted a population-based cohort study comparing the pregnancy outcomes after 22 weeks of women who conceived with a copper IUD that was removed, women with a retained IUD and pregnancies without an IUD. Deliveries occurred between the years 1991 and 2014. We used a multivariable generalized estimating equation (GEE) logistic regression model analysis to control for confounders and for maternal clusters, a Kaplan–Meier survival curve to compare cumulative neuropsychiatric hospitalizations incidence and a Cox proportional-hazards model to evaluate long-term neuropsychiatric hospitalizations.
*Results:* During the study period there were 221,805 deliveries, of which 203 (0.09%) and 149 (0.06%) occurred in patients with removed or retained copper IUD, respectively. Using GEE models, preterm delivery was independently associated with copper IUD use [odds ratio (OR) 2.1, 95% confidence interval (CI) 1.4–3.2 and OR 2.3, 95% CI 1.4–3.7 for removed and retained IUD, respectively]. We did not find an association between copper IUD presence or removal and the offspring's long-term neuropsychiatric hospitalizations (total long-term neuropsychiatric hospitalizations: 2.5%, 4.4% and 3.2% for removed, retained and no IUD, respectively, p=.71). Long-term neuropsychiatric hospitalization rate was comparable between the groups (Kaplan–Meier survival curve log rank p=.23).
*Conclusion:* Pregnancies in women who conceive with a removed or retained copper IUD are at an increased risk for short-term adverse perinatal outcomes, especially preterm delivery. For pregnancies that continued to at least 22 weeks, we found no benefit in IUD removal. However, the risk of long-term neuropsychiatric hospitalizations is not increased among offspring of these women.
*Implications:* Our data are insufficient to make a recommendation as to whether removal or retention of a copper IUD during pregnancy is best, as after 22 weeks' gestation we have found no benefit in IUD removal. Careful surveillance and categorization of the pregnancy as "high risk" are warranted.

## 1. Introduction

The intrauterine device (IUD) is the most commonly used reversible contraception method worldwide [1,2]. IUD use has increased in the United States during the last decade [3,4]. IUDs are a highly effective contraceptive option, with a failure rate comparable to permanent sterilization [5].

The pregnancy probability in the first year is 0.6% with perfect use and 0.5% to 0.8% with typical use [6–8]. While failure rates for both IUD types are low overall, the failure rates with progestin-releasing IUDs are somewhat lower than those of copper IUDs [8,9]. Other previously identified risk factors for IUD failure include young maternal age, IUD malposition and prior IUD expulsion [10].

Pregnancy with an IUD may involve several complications [11]. An earlier study published by our group, together with other studies, demonstrated that while maternal risk is primarily related to infection [11–13], fetal and neonatal risks include higher miscarriage rates, prematurity and lower Apgar scores [11–13]. A systematic review that included early and late pregnancy outcomes concluded that pregnancies conceived with an IUD that was not removed upon pregnancy diagnosis

were at greater risk of adverse pregnancy outcomes compared to pregnancies conceived with an IUD which was subsequently removed upon pregnancy diagnosis [14].

Many studies have described preterm birth as the major late adverse outcome in pregnancies conceived with an IUD [14].

Impaired neurodevelopmental outcome, and specifically cerebral palsy (CP), is a significant long-term complication associated with preterm birth. [15]. Perinatal researchers often use short-term neonatal morbidities as surrogate outcomes for long-term childhood neurological outcomes in preterm delivery studies. [16]. However, others claim that these associations are imprecise, perhaps because early alterations in brain maturation during fetal life, sociodemographic characteristics and other environmental factors mediate much of the longer-term neurological outcomes [17].

In light of the research describing pregnancy complications, such as preterm delivery and low Apgar scores, we opted to investigate both the perinatal outcomes and the long-term neuropsychiatric outcomes in children born to mothers who conceived with an IUD.

## 2. Materials and methods

### 2.1. Population and study design

We conducted a population-based study comparing all pregnancies in women with retained IUD, removed IUD and no IUD. Deliveries occurred between the years 1991 and 2014 at the Soroka University Medical Center (SUMC), which serves the entire population in Israel's Southern region.

The Institutional Review Board in accordance with the Helsinki declaration approved the study (protocol number 0438-15-SOR).

We collected data from two databases that were cross-linked and merged (merging was based on mother's and infant's identification numbers): the computerized perinatal database of the Obstetrics and Gynecology department and the computerized hospitalization database of the Pediatric department at SUMC.

The computerized perinatal database is constructed from information recorded immediately after each delivery by the attending obstetrician. The obstetrician reviews the medical charts and the delivery outcomes. Then, the files are transferred to professional medical secretaries, who enter the *International Classification of Diseases* (ICD) codes according to what the attending obstetrician recorded.

We subsequently based the study groups on ICD-9 coding: ICD-9 code v45.51 for deliveries in women with retained IUD, ICD-9 code z97.71 for deliveries in women who had an IUD removed early during pregnancy and a comparison group of deliveries in women who conceived with no IUD. Coding based on ICD codes was performed after careful evaluation of the medical prenatal care records, as well as the routine hospital documents. These procedures ensure the database's completeness and accuracy.

We included all singleton pregnancies of at least 22 weeks by last menstrual period. We did not have data regarding pregnancies ending before 22 weeks' gestation. Due to the theoretical interaction between offspring with congenital anomalies and other secondary outcomes such as low birth weight, low Apgar scores and long-term neurological morbidity, we excluded pregnancies in which offspring had congenital anomalies. We also excluded women lacking prenatal care due to lack of knowledge regarding this population's characteristics, specifically as it pertains to IUD use at conception time. We excluded cases of intrauterine fetal death, intrapartum death and neonatal demise cases from the long-term analysis.

We extracted information regarding clinical characteristics, obstetric risk factors, labor characteristics and perinatal outcomes from the computerized perinatal database of the Obstetrics and Gynecology department.

Our primary short-term outcome of interest was preterm delivery (for this reason, we restricted the study to singleton births). Other secondary short-term outcomes of interest were other pregnancy and neonatal complications such as placental abruption, low Apgar scores, intrauterine fetal death, intrapartum death and neonatal demise rates.

We defined clinical chorioamnionitis as the presence of uterine tenderness and/or purulent or malodorous amniotic fluid with any two of the following: antepartum temperature >37.8°C (100.4°F), maternal tachycardia (>120 beats/min), maternal leukocytosis (>18,000 cells/mm$^3$) or fetal tachycardia (>160 beats/min) [18]. We defined pathological presentation as nonvertex presentation. Intrauterine fetal death was defined as fetal death occurring after 20 weeks' gestation, while intrapartum death was defined as fetal death occurring during delivery, and neonatal demise was defined as an infant's death before 28 days of age.

We evaluated long-term neuropsychiatric morbidities after excluding cases of intrauterine fetal death, intrapartum fetal death and neonatal demise. Neuropsychiatric morbidity assessments included offspring hospitalizations until age 18 with any of the following diagnoses: movement disorders, CP, eating disorders, psychiatric disease, attention deficit hyperactivity disorder and developmental disorders (Supplemental Table 1). We grouped together the included diagnoses according to the ICD-9 coding.

We defined follow up time as time to an event (hospitalization) or until censoring. Censoring occurred in the case of death (during hospitalization), at 18 years old (which was calculated for each child based on date of birth) or at the end of the study period. We included only the first hospitalization in the analysis.

### 2.2. Statistical analysis

We performed the statistical analysis using SPSS software Version 23 (SPSS, Chicago, IL, USA) and STATA software Version 8 (StataCorp, College Station, TX, USA). We compared quantitative variables with normal distribution by Student's $t$ test. Categorical variables are shown in counts and percentages, and the differences were assessed by $\chi^2$ test (or Fisher's Exact Test as appropriate). We created dummy variables to compare women with retained IUD and after IUD removal versus mothers without copper IUD (reference).

For the short-term perinatal outcome analysis, we used a multivariable generalized estimating equation (GEE) logistic regression model analysis to control for confounders. Since several mothers delivered more than once during the study period, we controlled for similarity between siblings in the cohort. We adjusted for these similarities between siblings (i.e., maternal clusters) based on background and maternal characteristics. We considered variables as confounders if they were associated with the exposure and with the outcomes in the univariable level. All models controlled for maternal age, parity and hypertensive disorders. We tested the collinearity between the following covariables: maternal age, parity, hypertensive disorders (chronic or pregnancy related disorders) and diabetes mellitus (pregestational or gestational diabetes). Significant but weak correlations (all $r<0.17$) were found between the following variables: maternal age, hypertensive disorders or diabetes mellitus, parity and hypertensive disorders or diabetes mellitus, diabetes mellitus and hypertensive disorders. The correlation between parity and maternal age was moderate ($r=0.55$, p<.001); therefore, we included this variable in the final model.

After excluding fetal and neonatal deaths, we analyzed the long-term neuropsychiatric hospitalizations. We used Kaplan–Meier survival curve to compare cumulative incidence of neuropsychiatric pediatric hospitalizations. We used a Cox proportional-hazard model to estimate the adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) for long-term risk of neuropsychiatric pediatric hospitalizations while controlling for confounders. We considered a p value of <.05 as statistically significant.

## 3. Results

### 3.1. Short-term perinatal outcome of pregnancies conceived with an IUD

During the study period, a total of 261,508 deliveries occurred. After excluding multiple gestations ($n=11,454$), patients lacking prenatal

**Table 1**
Clinical characteristics of women with IUDs, after IUD removal and without IUD

| | Removed IUD n (%) 203 (0.09) | Retained IUD n (%) 149 (0.06) | No IUD n (%) 221,453 (99.84) | p value[a] |
|---|---|---|---|---|
| Maternal age, y | 30.8±5.4 | 30.8±4.9 | 28.4±5.8 | <.001 |
| Gestational age, wk | 38.4±2.9 | 38.4±2.8 | 39.1±1.9 | <.001 |
| Gravidity | | | | |
| 1 | 1 (0.5) | 1 (0.7) | 45,256 (20.4) | <.001 |
| 2–4 | 95 (46.8) | 52 (34.9) | 107,073 (48.4) | |
| 5≤ | 107 (52.7) | 96 (64.4) | 69,085 (31.2) | |
| Parity | | | | |
| 1 | 1 (0.5) | 1 (0.7) | 54,481 (24.6) | <.001 |
| 2–4 | 124 (61.1) | 63 (42.3) | 114,394 (51.7) | |
| 5≤ | 78 (38.4) | 85 (57.0) | 52,527 (23.7) | |

All data are presented as n (%) or mean ± standard deviation.
[a] Differences in categorical variables were assessed by $\chi^2$ tests. Differences in quantitative variables with normal distribution were compared by analysis of variance test.

**Table 3**
GEE models of risk factors for preterm delivery, chorioamnionitis, low birth weight and placental abruption

| Outcome | Characteristic | Adjusted OR | 95% CI |
|---|---|---|---|
| Preterm delivery | Removed IUD | 2.1 | 1.4–3.2 |
| | Retained IUD | 2.3 | 1.4–3.7 |
| | Maternal age | 1.2 | 1.1–1.3 |
| | Parity | 1.0 | 0.9–1.0 |
| | Hypertensive disorders | 2.8 | 2.7–3.0 |
| Clinical chorioamnionitis | Removed IUD | 8.0 | 4.2–15.2 |
| | Retained IUD | 4.5 | 16–12.2 |
| | Maternal age | 1.6 | 1.2–2.1 |
| | Parity | 1.0 | 0.9–1.0 |
| | Hypertensive disorders | 1.6 | 1.3–2.0 |
| Low birth weight | Removed IUD | 1.8 | 1. 2–2.9 |
| | Retained IUD | 2.4 | 1.4–4.0 |
| | Maternal age | 1.3 | 1.2–1.5 |
| | Parity | 0.9 | 0.91–0.93 |
| | Hypertensive disorders | 3.1 | 3.0–3.3 |
| Placental abruption | Removed IUD | 2.4 | 0.7–7.5 |
| | Retained IUD | 3.7 | 1.2–11.4 |
| | Maternal age | 1.0 | 0.8–1. 4 |
| | Parity | 1.0 | 1.05–1.09 |
| | Hypertensive disorders | 2.6 | 2.2–3.1 |

All models were adjusted to maternal age, parity and hypertensive disorders.
All data are presented as n (%) or mean ± standard deviation.

care (n=22,926) and cases of congenital malformations (n=5323), we included the remaining 221,805 deliveries in our analysis. Of 221,805 singleton gestations that occurred during the study period, 203 (0.09%) and 149 (0.06%) occurred in patients with a removed or retained IUD, respectively. For 300/352 (85%), the IUD type was available in the medical record; all were copper-based devices.

We compared congenital malformation and chromosomal abnormality rates in the neonates between the three groups (2.4%, 2.0% and 2.5% in removed IUD, retained IUD and no IUD, respectively, p=.93).

Since the study investigated deliveries occurring during a period of 23 years, we assessed the percentage of pregnancies conceived with a copper IUD over time. The prevalence of pregnancies conceived with a copper IUD has not changed during the study period (Supplementary Fig. 1).

Women who conceived with a copper IUD were older and had more past deliveries compared to the women who conceived with no IUD (Table 1).

When comparing obstetric risk factors and perinatal outcomes among the three groups, higher incidence of gestational diabetes mellitus and hypertensive disorders was found in the removed IUD group as compared to patients with retained IUDs or those who conceived without IUD. A direct comparison of short-term perinatal outcomes between removed and retained copper IUD demonstrated higher rates of hypertensive disorders among the removed IUD group (data not shown).

Table 2 provides the perinatal outcomes of the three groups. Mean gestational age for all preterm deliveries was 34.3±3.2 weeks (data not shown).

Intrauterine fetal death rates were comparable between the groups (0.5%, 0.0% and 0.3% in removed IUD, retained IUD and no IUD, respectively, p=.68). No intrapartum deaths were demonstrated among the retained or removed IUD groups compared to 48 cases in the no IUD group. Higher rates of neonatal demise occurred among the removed

and retained IUD groups (1.5%, 1.3% and 0.2% in removed, retained and no IUD, respectively, p<.001).

Table 3 gives results of the GEE analyses. Restricting the analyses to vaginal deliveries yielded similar results (Supplementary Table 2).

We stratified the same GEE models to term and preterm births separately. While both removed and retained copper IUDs were no longer associated with low birth weight and placental abruption, the association with chorioamnionitis remained significant (data not shown).

### 3.2. Offspring long-term neuropsychiatric hospitalizations

After excluding deliveries with fetal or neonatal deaths, 220,709 deliveries were included in the long-term analysis, of which 199 (0.09%) and 147 (0.06%) were pregnancies with removed and retained copper IUDs, respectively. We used two different models to assess the trends of neuropsychiatric-related hospitalization within the study period. Hospitalization rates were stationary, with neither linear nor polynomial trends over the study period.

Children born to mothers who conceived with a copper IUD did not have higher long-term neuropsychiatric hospitalization incidence as compared to children born to mothers who conceived without an IUD (Table 4). No cases of cerebral palsy, eating disorders, psychiatric disease, attention deficit hyperactivity disorder or developmental delay were identified among offspring of women with removed or retained copper IUD.

We compared the cerebral palsy rates between term and preterm deliveries. As would be expected, rates of CP were higher among preterm than term offspring (0.3% vs. 0.1%, p<.001).

**Table 2**
Perinatal outcomes of pregnancies with and without IUD; comparison between three groups and direct comparison between removed and retained IUD

| | Removed n (%) 203 (0.09) | Retained IUD n (%) 149 (0.06) | No IUD n (%) 221,453 (99.84) | p value[a] | p value[b] |
|---|---|---|---|---|---|
| Preterm birth | 29 (14.3) | 21 (14.1) | 14,993 (6.8) | <.001 | .95 |
| Clinical chorioamnionitis | 10 (4.9) | 4 (2.7) | 1329 (0.6) | <.001 | .28 |
| Placental abruption | 3 (1.5) | 3 (2.0) | 1184 (0.5) | .01 | <.001 |
| Induction of labor | 46 (22.7) | 34 (22.8) | 60,415 (27.3) | .15 | .70 |
| Cesarean section | 53 (26.1) | 26 (17.4) | 31,018 (14.0) | <.001 | .82 |
| Low birth weight | 23 (11.3) | 18 (12.1) | 14,524 (6.6) | .001 | .05 |

All data are presented as n (%) or mean ± standard deviation.
[a] Differences between three groups, assessed by $\chi^2$ tests.
[b] Direct comparison between pregnancies conceived with removed and retained IUD, assessed by $\chi^2$ tests.

**Table 4**
The association between pregnancy with IUD and long-term neuropsychiatric hospitalizations of the offspring

| Offspring long-term neuropsychiatric morbidity | Removed IUD n (%) 199 (0.09) | Retained IUD n (%) 147 (0.06) | No IUD n (%) 220,363 (99.84) | p value |
|---|---|---|---|---|
| Movement disorders | 4 (2.0) | 5 (3.4) | 4142 (1.9) | .39 |
| Other neuropsychiatric disorders | 0 (<0.1) | 1 (0.7) | 842 (0.4) | .57 |
| Total neuropsychiatric hospitalizations | 5 (2.5) | 6 (4.1) | 6995 (3.2) | .71 |

All data are presented as n (%) or mean ± standard deviation.

Using a Kaplan–Meier curve, the cumulative incidence of neuropsychiatric hospitalizations among children born to mothers who conceived with and without a copper IUD was similar (log-rank test p=.23).

In the Cox regression analysis, after adjusting for maternal age, diabetes and hypertensive disorders, pregnancy conceived with a copper IUD did not exhibit an independent association with offspring long-term neuropsychiatric hospitalizations (aHR 0.6, 95% CI 0.2–1.5, p=.33 and aHR 1.8, 95% CI 0.8–4.0, p=.15 for removed and retained IUD, respectively, Supplementary Table 3).

## 4. Discussion

Our study's major finding is that pregnancies conceived with a copper IUD in situ are associated with adverse short-term perinatal outcomes but not with offspring long-term neuropsychiatric hospitalizations. Our study found an association between both removed and retained copper IUDs and adverse pregnancy outcomes such as preterm delivery and clinical chorioamnionitis, as well as an association between retained IUD and placental-related adverse pregnancy outcomes such as low birth weight and placental abruption. However, in direct comparison of the removed IUD and the retained IUD groups, the outcomes (preterm delivery, clinical chorioamnionitis, low birth weight and placental abruption) were similar.

The IUD type was documented for 300 of 352 women who conceived with an IUD, and all were copper based devices. Thus, we assumed that most of the unknown IUD types are likely copper-based devices as well. As copper-based IUDs cause a different inflammatory response than hormonal IUDs, our study is mainly about outcomes with copper-based IUDs.

In agreement with other studies, both removed and retained copper IUDs were found to be independent risk factors for preterm delivery and chorioamnionitis. Indeed, histopathologic reports of placentas from pregnancies conceived with an IUD revealed signs of ascending infection (endometritis) and inflammation (subchorionic hemorrhage and decidual edema) [18,19]. Hence, the reactive inflammation caused by foreign body presence (i.e., the IUD) resulted in preterm delivery and clinical chorioamnionitis [18]. In our study, the IUD removal in early pregnancy did not eliminate the risk of preterm birth and chorioamnionitis compared to pregnancies conceived without an IUD. The association between pregnancies conceived with an IUD and the risk of preterm delivery was also noted in previous studies [20–22]. Nevertheless, our cohort allows for the investigation of obstetric parameters that have not been previously examined in large study groups, such as placental abruption and low birth weight. Moreover, unlike most other studies, we included three comparison groups and in this way were able to demonstrate pregnancy outcomes among women with removed or retained copper IUDs.

It should be noted that the main difference between retained, removed and no IUD is the duration of exposure to the IUD. As in other exposures, the dose–response concept distinguishes between 8 months of in utero exposure to the IUD in cases of retained IUDs versus lower exposure in cases of removed IUDs, and no exposure in cases of no IUD. Nevertheless, in our study, we had limited ability to assess the effect of longer IUD exposure because we did not have information regarding the timing of IUD removal.

Other observational studies have shown that women who conceived with an IUD have higher relative risk of giving birth to underweight infants [22]. Our study also revealed an association between retained copper IUDs and low birth weight, as well as placental abruption. It can be speculated that the mechanism of placenta-associated disorders is an abnormal placentation and hostile intrauterine environment caused by the retained copper IUD.

The study's strengths lie within its large cohort. Our estimations are based on a computerized database, which included a large sample size from a single tertiary medical center, thereby decreasing the likelihood of incorrect outcome data. Moreover, our dataset combines prenatal, neonatal and long-term offspring data, enabling the unique opportunity to examine the long-term neuropsychiatric outcome of offspring following pregnancy conceived with a copper IUD, with the ability to control for parameters surrounding pregnancy and delivery. Nonetheless, our statistical power to assess the long-term outcomes was limited.

Since IUD removal after pregnancy diagnosis is not performed at the hospital but rather in an outpatient setting, we did not have information regarding the timing of IUD removal.

Important adverse outcomes of pregnancies conceived with an IUD are first-trimester losses and ectopic pregnancies [14]. Our study focused on pregnancy outcome beyond viability. Since we included only pregnancies after 22 weeks' gestation, this study cannot assess whether IUD removal affects pregnancy outcomes before 22 weeks.

In conclusion, women conceiving with a copper IUD are at an increased risk for adverse short-term perinatal outcomes, especially preterm delivery. Our data are insufficient to make a recommendation as to whether IUD removal or retention during pregnancy is best.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.04.005.

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