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The intrauterine device and ectopic pregnancy

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Abstract

Based on data given by case-control and cohort studies the relationships between current and past IUD use, duration of IUD use and the type of IUD were evaluated to determine the risk of ectopic pregnancy among IUD users. The results of this review indicate that current and past IUD users do not have an increased risk of ectopic pregnancy. No relationship was found between the duration of IUD use, for either current or past IUD users, and the risk of ectopic pregnancy. Pooled data from clinical studies of different types of IUD showed that the lowest risk of ectopic pregnancy was for users of copper-bearing IUDs, and the highest risk was for users of progesterone-releasing IUDs. Further research is needed to evaluate the ectopic pregnancy risks to past IUD users, especially in view of recent studies which have shown that these women may be at a higher risk of infertility.

Introduction

In 1965, Lippes [1] reported 4 ectopic pregnancies (17.4%) among 23 women who had become pregnant with a Lippes Loop *in situ*. Since the ectopic pregnancy rate in the general population in the United States in 1965 was estimated to be about 1 in 289 pregnancies (0.4%) [2], there was concern that IUD use might significantly increase the risk of ectopic pregnancy. The uniform finding of researchers who have investigated the incidence of ectopic pregnancy in the United States is that during the 1970s its incidence increased [2–8]. Since 1965, numerous reports have provided data on the risk of ectopic pregnancy to IUD users and have discussed whether IUD use has contributed to the increasing incidence of ectopic pregnancy. Even with the extensive work which has been done on this topic, there are still some unanswered or only partially answered questions relating to the use of IUDs and the risk of ectopic pregnancy, including the following:

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1. Is the incidence of ectopic pregnancy in IUD users similar to that in women using no method of contraception?
2. Do women who discontinue IUD use have a similar incidence of ectopic pregnancy compared to non-contraceptors?
3. Is the incidence of ectopic pregnancy similar for users of different types of IUD who become pregnant with their IUDs *in situ*?

In the following sections of this report these questions are evaluated.

Incidence of ectopic pregnancy: IUD users versus non-users

Although the risk of ectopic pregnancy to IUD users has been evaluated in many publications [9], there is little information available on the relative risks of ectopic pregnancy for IUD users compared to non-users of IUDs or users of other methods of contraception. Three studies have evaluated this issue: the Women's Health Study (WHS), the Oxford Family Planning Association study in the UK, and a multiclinic, international study conducted by the World Health Organization (WHO).

The WHS was a large case-control study conducted at 16 hospitals in 9 cities in the United States in 1976–78. The study was designed to estimate the relative risks of gynecologic and obstetric complications severe enough to require hospitalization for women using IUDs. The results of the WHS have been published in at least 8 papers, including one on ectopic pregnancy [10]. As a case-control study, the WHS did not provide data on the incidence of ectopic pregnancy in IUD users versus non-users of IUDs. A reanalysis of some of the data from the WHS is given in Table 1. This shows that women who were using IUDs at the time of their last menstrual period, i.e. pregnancy occurred while they were using IUDs, and who

Table 1 Relative risk of ectopic pregnancy for IUD users versus never users of IUDs by duration of IUD use and years from last use

Time from last use of IUD	*Duration of IUD use (years)*							
	<2		2-4		>4		*All**	
	RR	95% *CL*	*RR*	95% *CL*	*RR*	95% *CL*	*RR*	95% *CL*
Used at last menstrual period	0.49	0.30,0.79	1.0	0.57,1.8	1.7	1.3,2.2	1.2	0.91,1.5
Used in last year but not at last menstrual period	0.97	0.58,1.6	1.9	0.81,4.4	2.2	1.3,3.8	1.4	0.98,2.0
Used more than one year previously	1.2	0.83,1.8	1.8	0.78,4.2	0.72	0.25,2.0	1.2	0.86,1.7

RR = relative risk; CL = confidence limits
*Mantel-Haenszel estimate adjusted for duration of IUD use

had used their IUDs for less than 2 years had significantly ($p<0.05$) lower risk of ectopic pregnancy (relative risk = 0.49) compared to women who had never used IUDs. This relative risk increased to 1.7 ($p<0.05$) for women who used their IUDs for 4 or more years. The comparison group included non-contraceptors and women using contraceptive methods other than IUDs. This group may be an inappropriate control group for the determination of the relative risks to women who have used IUDs for different periods of time. Regardless of the duration of IUD use, overall IUD users were not found to be at any increased risk of ectopic pregnancy (relative risk = 1.2) ($p>0.05$).

The study conducted by WHO [11] was also a case-control study and evaluated the relative risk of ectopic pregnancy to users of different contraceptive methods compared to non-contraceptors. The study was conducted at clinics in developing and developed countries and included 2 control groups; one included only non-pregnant women and the other included only pregnant women. The estimated relative risks and their 95% confidence limits derived from this study are given in

Table 2 Relative risk (RR) and 95% confidence limits of ectopic pregnancy to IUD users compared to non-contraceptors

Controls	*Developing countries*	*Developed countries*
	RR 95% CL	*RR 95% CL*
Non-pregnant	0.4 (0.2,0.6)	0.6 (0.3,1.3)
Pregnant	5.7 (2.7,12.1)	12.2 (3.0,49.7)

Source: Gray [11]

Table 2. The study shows a decreased risk of ectopic pregnancy to IUD users in developing countries based on the analyses using the non-pregnant controls. When the relative risks are estimated using the pregnant controls, who were probably less likely to be using any method of contraception when pregnancy occurred, IUD users are shown to have a significantly increased risk ($p<0.05$) of ectopic pregnancy. The study did not provide estimates of the relative risk of ectopic pregnancy for different durations of IUD use. When all of the results are considered, the study does not indicate that current use of IUDs increases the risk of ectopic pregnancy.

The study conducted by the Oxford Family Planning Association found that current IUD users had significantly higher ($p<0.05$) ectopic pregnancy rates (0.121 per 100 woman years) compared to either oral contraceptive (0.001 per 100 woman years) or diaphragm users (0.010 per 100 woman years) [12]. Since this study did not provide data on the incidence of ectopic pregnancy in women not using any method of contraception, no conclusions can be derived except that IUDs are less effective in preventing ectopic pregnancy than some other methods of contraception.

Three other reports [13–15] have provided data on the risks of ectopic pregnancy to IUD users as a function of the duration of IUD use. Vessey and co-workers [15], using data from the Oxford Family Planning Association study, found that the rate

of ectopic pregnancy showed no clear relationship to the duration of IUD use for women who used their IUDs for up to 7 or more years. The overall rate was 0.12 ectopic pregnancies per 100 woman years of IUD use. The same study showed that the rate of intrauterine pregnancy decreased with increasing duration of IUD use, from 2.6 pregnancies per 100 woman years for women who used their IUDs for 18 months or less to 0.97 pregnancies per 100 woman years for women who used their IUDs for 91 months or more. While the rate of ectopic pregnancy was fairly constant over time, the proportion of all pregnancies that were ectopic increased over time: 3.1% for IUD use of ≤36 months; 9.9% for IUD use of 37–72 months; and 12.0% for IUD use of 73 months or more. Consistent with these data are those presented by Jain [13] and Tatum and Schmidt [15], who reported that the rate of ectopic pregnancy calculated as a percentage of total pregnancies increased with increasing duration of IUD use.

There are no apparent reasons for the lack of agreement between the results of the WHS and other studies [13–15] that evaluated the risk of ectopic pregnancy and the duration of IUD use. In the WHS the duration of IUD use was not obtained from clinical records, but was based on the recall of the cases (women with ectopic pregnancy) and controls (non-pregnant women). Inaccuracies in the recall of cases and controls may have contributed to the inconsistent findings. The question of whether or not the duration of IUD use increases the risk of ectopic pregnancy will require further evaluation.

Risk of ectopic pregnancy to past IUD users

The conception rates of women who discontinue IUD use in order to conceive have been evaluated in many studies. These studies are usually limited to providing information on conception rates for users of different types of IUD, and do not generally provide information on pregnancy outcomes. Little information has been published on the outcomes of pregnancies in past IUD users compared to users of other contraceptive methods.

Table 1 presents data from the WHS and gives estimates of the relative risk of ectopic pregnancy to past IUD users who discontinued IUD use in the year before, and more than one year before admission for treatment of an ectopic pregnancy. The data in Table 1 suggest that the risk of ectopic pregnancy to past IUD users increases with the duration of IUD use. However, the only relative risk that was significantly increased ($p<0.05$) was for women who used IUDs for more than 4 years and who discontinued IUD use within the year before hospital admission. The control group used in the WHS may be inappropriate for the determination of the relative risks to past IUD users who used IUDs for different periods of time. Regardless of the duration of IUD use, prior IUD use did not increase the risk of ectopic pregnancy ($p>0.05$) (Table 1).

For women who stopped their method of contraception in order to conceive, the Oxford Family Planning Association data [16] show no increased risk of ectopic pregnancy (calculated as a percentage of all pregnancies) for prior IUD users compared to prior users of oral contraceptives and other methods. The following

ectopic pregnancy rates were obtained: oral contraceptors, 0.25% (2029 pregnancies); IUD users, 0.0% (226 pregnancies); and users of other methods, 0.13% (2263 pregnancies).

Considered collectively, the studies reviewed do not indicate that past IUD use, regardless of the type of IUD used, increases a woman's risk of ectopic pregnancy.

Ectopic pregnancy incidence for users of different types of IUD

The issue of the risk of ectopic pregnancy to users of different types of IUD was first raised in 1977 by Snowden [17] who noted that the Progestasert IUD appeared to be associated with a higher ectopic pregnancy rate, based on data reported by the manufacturer, compared to other types of IUD. In 1978, the Food and Drug Administration (FDA) convened a special meeting to evaluate the ectopic pregnancy rates associated with the use of different types of IUD. Ectopic pregnancy rates associated with the use of different types of IUD based on data presented to

Table 3 Ectopic pregnancy rates (per 100 woman years) for different IUDs

IUD	*Woman years of use*	*Ectopic pregnancy rate*
Progestasert	10567	0.40
Non-medicated	28614	0.12
TCu	11036	0.05
Cu-7	13135	0.04

Source: FDA Drug Bulletin [18]

the FDA are given in Table 3. These data show that users of copper-bearing IUDs have the lowest risk of ectopic pregnancy and users of the Progestasert have the highest risk of ectopic pregnancy.

Since ectopic pregnancy is a relatively rare event, no one study can be expected to provide estimates of ectopic pregnancy rates to users of different types of IUD which have been widely used in the United States. To obtain these estimates, over 1000 studies on IUDs were reviewed. The data from these studies were pooled to give an overall estimate of ectopic pregnancy rates (per 100 woman years of IUD use) for users of different types of IUD (Table 4). There is little difference between

Table 4 Ectopic pregnancy rates (per 100 woman years) for various IUDs

Type of IUD	*Number of studies*	*Woman years of IUD use*	*Ectopic pregnancy rate*
Cu-7	13	27646	0.08
TCu (all models)	16	30959	0.09
Dalkon Shield	17	17944	0.11
Lippes Loop	14	33753	0.13
Saf-T-Coil	3	4839	0.09
Progestasert	9	6893	0.38

the rates for the copper-bearing and non-medicated IUDs (0.08 vs. 0.12 per 100 woman years), and both of these rates are substantially lower than the Progestasert rate (0.38 per 100 woman years). The rate for the Progestasert was virtually unchanged if the data originally presented by the manufacturer [19] were either included or excluded.

Although the numbers of users of some specific types of IUD in the WHS are quite small, the study can still be used to provide estimates of the relative risks of ectopic pregnancy to users of different types of IUD compared to women who have

Table 5 Relative risk of ectopic pregnancy to users of different types of IUDs versus never users of IUDs

Type of IUD	*IUD used at last menstrual period*		*IUD used in last year but not at last menstrual period*	
	RR	*95% CL*	*RR*	*95% CL*
Cu-7	0.73	0.46,1.2	1.4	0.71,2.7
Dalkon Shield	1.1	0.32,3.8	0.85	0.10,6.9
Lippes Loop	1.1	0.65,1.7	1.2	0.49,2.9
Progestasert	0.94	0.28,3.2	+	+ +
Saf-T-Coil	0.66	0.15,2.8	0.66	0.09,5.1
TCu	0.54	0.07,4.1	0.85	0.10,6.9
All*	0.80	0.61,1.1	1.3	0.85,2.0

RR = relative risk; CL = confidence limits
+Insufficient data
*Includes all types of IUD including unknown types

never used IUDs (Table 5). Neither current IUD use (IUD used at last menstrual period) nor past IUD use (IUD used in last year) was associated with either a higher or lower relative risk of ectopic pregnancy for users of any type of IUD. The data neither showed nor suggested a higher risk of ectopic pregnancy for users of the Progestasert.

There were too few users of specific types of IUD in the WHS to evaluate the relative risks of ectopic pregnancy for both IUD type and duration of IUD use. However, the data did not suggest any duration of use effect. As expected, most current and past users of Cu-7, Progestasert and TCu IUDs had used their IUDs for less than 3 years, compared to 3 or more years for Dalkon Shield users. The relative risks of ectopic pregnancy for users of these types of IUD were similar for current and past users.

Another case-control study [20] found that past users of the Dalkon Shield had a higher risk of ectopic pregnancy compared to users of other types of IUD (Cu-7, Lippes Loop, Progestasert, Saf-T-Coil, TCu). In this unpublished study, no information was presented on the duration of IUD use or the elapsed time interval from last IUD use to the occurrence of ectopic pregnancy. Since Dalkon Shields were not inserted after 1975, it is likely that the average time between last use of an IUD and the occurrence of ectopic pregnancy was longest for past Dalkon Shield users, and shortest for past users of the Cu-7, Progestasert and TCu IUDs, which

were not commercially available until after mid-1974. In the time period between last use of an IUD and ectopic pregnancy, women were exposed to factors other than IUD use which may increase their risk of ectopic pregnancy. The longer this time period, the higher the risk of exposure to these factors and the higher the risk of ectopic pregnancy. Indirectly, this is borne out by data from the United States [8] showing that from 1970 to 1978 ectopic pregnancy rates increased with age for both whites and non-whites.

Comment

There are some discrepancies between the results of case-control studies and other types of clinical studies which have evaluated various aspects of the risks of ectopic pregnancy to current and past IUD users. Of the case-control studies, only one [20] found an increased risk of ectopic pregnancy for past IUD users (Dalkon Shield users). In contrast, the WHS (also a case-control study) found a similar risk of ectopic pregnancy to current and past users of all types of IUD. The pooled results of clinical studies which have provided data on the incidence of ectopic pregnancy in current IUD users generally point to a slightly lower incidence for users of copper-bearing IUDs and a significantly higher incidence for users of the Progestasert, a progesterone-releasing IUD. These data cannot be used to infer any cause-and-effect relationship between IUD use and the risk of ectopic pregnancy. The data does imply that different types of IUD have different effectiveness rates in terms of their ability to prevent ectopic pregnancies. In this regard, it seems that the copper-bearing IUDs are most effective and the progesterone-releasing IUD is the least effective.

Based on the various studies and data that were evaluated in this paper the following may be concluded:

1. Neither current nor past use of an IUD is associated with any increased risk of ectopic pregnancy.
2. The incidence of ectopic pregnancy appears to be similar for current users of all types of IUD, except for the Progestasert.
3. The duration of IUD use does not increase the risk of ectopic pregnancy.

Two recently published case-control studies [21, 22] reported that past IUD use was associated with an increased risk of primary tubal infertility. Those factors that are associated with an increased risk of tubal infertility, e.g. prior pelvic inflammatory disease (PID), may also increase the risk of ectopic pregnancy to women who have used IUDs. However, the present study based on the review of different types of studies found no conclusive evidence for an increased risk of ectopic pregnancy to past IUD users.

Many investigators who have evaluated the risks of PID to users of different types of contraceptive methods have concluded that IUD users have a higher risk of PID compared to users of other contraceptive methods [9]. The medical literature generally acknowledges that PID increases the likelihood of an ectopic pregnancy. Since IUDs are not always removed following the diagnosis of suspected PID and since women may also have subclinical PID which is undiagnosed, current IUD

users and past IUD users should be at a higher risk of ectopic pregnancy. This was not the finding of the present review. The lack of consistency among studies clearly points to the need for further evaluation of the interrelationships between contraceptive use and predisposing factors, such as pelvic inflammatory disease, to tubal infertility and ectopic pregnancy.

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Resumé

A partir de données obtenues par contrôle de cas individuels et études de cohortes, on a évalué les rapports entre l'emploi actuel et passé des stérilets, la durée d'emploi et le type des stérilets utilisés dans le but de cerner les risques de grossesse extra-utérine chez les utilisatrices de stérilets. Les résultats de ces études indiquent que le risque de grossesse extra-utérine n'augmente pas chez les femmes ayant utilisé ou utilisant un stérilet. Il n'a été découvert aucun rapport entre la durée d'emploi du stérilet – actuel ou passé – et les risques de grossesse extra-utérine. Les données regroupées en provenance d'études clinques portant sur divers types de stérilet ont révélé que le risque de grossesse extra-utérine était moindre chez les utilisatrices de stérilets contenant du cuivre, et était le plus élevé chez les femmes portant des stérilets à dégagement de progestérone. Il faudra procéder à des recherches plus approfondies afin d'évaluer le degré de risque de grossesse extra-utérine chez les femmes ayant utilisé des stérilets dans le passé, d'autant plus que des études récentes ont révélé que ces femmes pourraient éventuellement courir un risque accru de stérilité.

Resumen

Basado en datos proporcionados por estudios de casos-controlados y de cohortes se evaluaron las relaciones entre el uso presente y pasado de DIU, la duración de uso, y el tipo de DIU, a fin de determinar el riesgo de embarazo ectópico entre las portadoras de DIU. El resultado de esta revisión indica que las usantes pasadas y presentes de DIU no tienen un riesgo aumentado de embarazo ectópico. No se observó ninguna relación entre la duración de uso de DIU, el uso presente o pasado de DIU y el riesgo de embarazo ectópico. Datos agrupados de estudios clínicos de diferentes tipos de DIU mostraron que el más bajo riesgo de embarazo ectópico fue para los DIU con cobre y que el más alto riesgo para los DIU liberadores de progesterona. Más investigación es necesaria para evaluar los riesgos de embarazo ectópico en usuarias antiguas de DIU, especialmente, desde que estudios recientes han demostrado que estas mujeres podrían sufrir un más alto riesgo de infertilidad.