Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects

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There are many potential mechanisms of action for the intrauterine device (IUD), which vary by type of IUD (inert, copper, or hormonal). This paper reviews the evidence for each potential mechanism of action. On the basis of available data for fertilization rates and clinical pregnancy rates, the relative contribution of mechanisms acting before or after fertilization were quantitatively estimated. These estimates indicate that, although prefertilization effects are more prominent for the copper IUD, both prefertilization and postfertilization mechanisms of action contribute significantly to the effectiveness of all types of intrauterine devices. (Am J Obstet Gynecol 2002;187:1699-708.)

Key words: Intrauterine contraceptive devices, mechanism of action, contraception

There is ongoing controversy regarding the mechanisms of action of the intrauterine device (IUD) in humans. Classically, the view was that the IUD in humans acted predominantly after fertilization to prevent implantation,[1,2] but evidence has accumulated for important contributions of effects before fertilization.[3-6] In 1997, a review suggested that effects that occur after fertilization are an important mechanism of action in all types of IUDs,[7] but this conclusion was disputed for copper IUDs.[8-11] Since this time, at least three reviews have suggested that the contraceptive effects of the copper IUD occur predominantly before fertilization.[12-14] In the meantime, a new type of IUD (levonorgestrel) has become available in the United States.[15]

Understanding the mechanisms of action of the IUD in humans is important for fundamental biomedical knowledge. It also provides key information for clinicians who work with patients who may object to forms of birth control that act after fertilization.[16,17] The purpose of this paper is to review published data on the mechanisms of action of the IUD and to estimate the contribution of prefertilization and postfertilization mechanisms of action for the different types of IUDs that are in common clinical use, using a mathematic model based on published physiologic data. By prefertilization effects, we mean all contraceptive effects that reduce the probability of fertilization. By postfertilization effects, we mean all effects that operate after fertilization to reduce the probability of clinically recognized pregnancy.

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Methods

We conducted iterative searches of MEDLINE and POPLINE from 1966 to the present to identify articles published in peer-reviewed medical literature that provided data or reviews of the mechanism of action of the IUD. We reviewed the references section of the articles to identify additional articles. We developed a mathematic model of prefertilization and postfertilization effects based on physiologic principles and applied the parameters that were known or estimated from the literature to this model. This yielded estimates of the outcome parameters of the contributions of prefertilization and postfertilization effects toward the efficacy of different types of IUDs.

Proposed mechanisms of action

The mechanisms of action of the IUD vary considerably among different animal species, and therefore the results of animal studies cannot be used to define the mechanisms of action in humans.[1,3] Further, multiple mechanisms of action are likely to operate in humans.[4] The possible mechanisms of action for the IUD in hu-

mans can each be classified as occurring before or after fertilization.[18] The possible prefertilization mechanisms of action of the IUD include the following: inhibition of sperm migration and viability at the level of the cervix, endometrium, and tube; slowing or speeding the transport of the ovum through the fallopian tube; and damage to or destruction of the ovum before fertilization. Hormonal evidence indicates that the IUD does not generally inhibit ovulation in humans.[3,19-23] The majority of women who are wearing hormonally active IUDs that reduce or eliminate menstruation still have ovulatory cycles as assessed by hormonal measurement and follicular ultrasonography.[15,22,24-27] The possible postfertilization mechanisms of action of the IUD include the following: slowing or speeding the transport of the early embryo through the fallopian tube, damage to or destruction of the early embryo before it reaches the uterus, and prevention of implantation.

Sperm transport through the cervical mucus and the endometrium

Biochemical changes in the cervical mucus have been noted with all types of IUDs,[28,29] but sperm penetration does not seem to be affected substantially by inert IUDs.[30,31] Oral or systemic progestins are known to alter cervical mucus and theoretically should inhibit sperm transport through the cervix.[28,32,33] However, in a recent study of long-term users of levonorgestrel IUDs, 69% of the ovulatory cycles had cervical mucus favorable for sperm transport.[22] In contrast, copper IUDs raise the copper concentration of cervical mucus substantially,[29] and this has been shown to inhibit sperm motility.[31] In contrast to cervical mucus, there is abundant evidence for endometrial changes that are likely to be to some degree spermicidal, inhibiting sperm migration through the endometrium for all types of IUDs.[5,12] The higher inflammatory response of the endometrium in the presence of copper IUD suggests that copper IUDs may have a stronger spermicidal effects on the endometrial level.[5,12] There may be some reduction in the fertilization potency of sperm with the copper IUD. In vitro studies have suggested that copper ions inhibit sperm motility but not necessarily fertilizing capacity.[31,34] In levonorgestrel IUDs, the atrophy and decidualization of the glands may also inhibit sperm survival.[12,35]

Sperm recovery from fallopian tubes

A number of investigators have attempted to recover spermatozoa from the fallopian tubes from IUD users and sometimes also from control subjects. These data are summarized in Table I.[4,30,36-38] We have also calculated CIs.[39] These studies attempted sperm recovery 2 or more hours after insemination. Not included in Table I are a study that examined only early sperm transport in IUD users (15-30 minutes after insemination)[40] and a study that had insufficient detail regarding the sperm recovery procedures.[41]

Most reports do not have a detailed description of factors that may influence the recovery of sperm from the fallopian tube. However, there does seem to be a trend that when a smaller proportion of women with IUD had sperm in the tubes, so did a smaller proportion of controls, suggesting that there is variability in the sensitivity of the procedures used between studies (Table I). Some reports have attempted to quantify the number of sperm recovered, but lack of detail of these same factors makes it impossible to compare numbers of spermatozoa among studies.

Recovery of ova

Ova have been recovered from the fallopian tubes by flushing in approximately 65% of cycles of normally fertile women not using contraception.[45-47] Alvarez et al used this method at the time of gynecologic surgery to examine women using various IUDs as well as control women using no contraception.[6,48] They recovered ova in 64 of 115 control women (56%), 7 of 15 women with inert IUDs (47%), 8 of 27 women with copper IUDs (30%), and 7 of 14 women with progestin IUDs (both progesterone and levonorgestrel, 50%). These data suggest that copper IUDs (but not inert or progestin IUDs) may have an ovicidal effect and therefore may also be more likely to destroy a fertilized ovum. This is consistent with data suggesting that the concentration of copper in fluid from the fallopian tube is similar to the concentration in fluid from the uterine cavity.[48]

Morphologic evidence of fertilization

The available evidence on the direct observation of fertilized ova in the fallopian tubes of IUD users are limited to two studies. Through an extensive search in women who were undergoing gynecologic surgeries, Clewe et al recovered ova from five IUD users, one of whom showed evidence of having been fertilized and undergoing normal development.[42,49] In the previously mentioned study by Alvarez et al,[48] 20 controls and 14 IUD users from whom ova were recovered had intercourse around the surge of luteinizing hormone. These ova were examined by light and electron microscopy for evidence of fertilization.[48] Another examination of the same ova (except for three from the women without IUDs) was conducted by Ortiz et al.[3] Their final results are summarized, along with those from the study of Clewe et al,[49] in Table II, together with CIs that we have calculated.

It is possible that in these studies there was a systematic bias toward recovery of ova that are fertilized because such ova are likely to be viable or recoverable for a longer period of time.[45] However, this bias should be equally as operative in control women as in women with IUDs. Therefore, the relative difference between the two groups

Table I. Recovery of spermatozoa from fallopian tubes during use of various IUDs

		IUD users		*Controls without IUDs*	
Type of IUD	*Study*	*No. of cases with spermatazoa present/ Total cases*	*Proportion of cases with spermatazoa present (95% CI)*	*No. of cases with spermatazoa present/ Total cases*	*Proportion of cases with spermatazoa present (95% CI)*
Inert IUD	Brown and Allen (1966)[36]	6/6	1.0 (0.54-1.0)	6/6	1.0 (0.54-1.0)
	Malkani and Sujan (1964)[30]	4/4	1.0 (0.40-1.0	—	—
	Noyes et al (1966)[42]	6/10	0.60 (0.26-0.88)	—	—
	Aref (1983)[43]	7/10	0.70 (0.35-0.93)	11/15	0.73 (0.45-0.92)
	El Habashi et al (1980)[37]	0/30	0.0 (0.0-0.12)	14/30	0.47 (0.28-0.66)
Copper IUD	Croxato (1973)[44]	4/6	0.67 (0.22-0.96)	13/17	0.76 (0.50-0.93)
	Aref (1983)[43]	0/5	0.0 (0.0-0.52)	11/15	0.73 (0.45-0.92)
		0/13	0.0 (0.0-0.25)	10/20	0.50 (0.27-0.73)
Hormonal IUD	No data				

can be expected to be a reasonable reflection of the proportional difference in the absence of any recovery bias.

Biochemical evidence for fertilization

The earliest available biochemical marker of fertilization in humans in vivo is early pregnancy factor (EPF). EPF is not unique to pregnancy, but it can be detected as early as 1 to 2 days after fertilization and continuing through most of the pregnancy as long as it remains viable.[53] Studies in humans have used the rosette inhibition test to measure EPF, a bioassay that has a complex dose-response profile that has in the past yielded apparently conflicting study results.[54,55] More recently, EPF has been characterized as a protein that is a close homolog to chaperonin-10 and seems to have a key role in rapid cell proliferation.[56] EPF is consistently not detected in women who do not have the possibility of conception, suggesting a high specificity for fertilization.[51,52,57] Sensitivity is less clear. Some investigators have found false-negative EPF results in pregnancies in women being treated for infertility or with recurrent spontaneous abortion.[58,59] However, in the majority of early pregnancies that are detected by human chorionic gonadotropin (hCG) or ultrasound but that also have negative EPF, the pregnancy is nonviable, resulting in spontaneous abortion.[58-60] Additionally, other studies have found no false-negative results among women being treated for infertility.[61,62] A recent study found a 3.4% false-negative rate in 70 couples of apparently normal fertility who were striving to achieve pregnancy.[52] Table II summarizes the results of three separate studies of EPF with documented intercourse around ovulation, three in women not using contraception[50,52,63] and one in women with inert or copper IUDs.[51] Although these results come from separate studies and the use of EPF to detect fertilization is not fully established, it is reassuring that they are concordant with the data reported from direct observation of ova.

The most widely used biochemical marker of pregnancy is β-hCG. Most studies that have measured hCG in IUD users suggest that hCG is detectable in fewer cycles from women with IUDs than from women without IUDs.[3,64,65] However, hCG first becomes detectable relative to background levels in control subjects around the time of implantation. In a study that identified the day of ovulation by ultrasound in women trying to get pregnant, hCG was never detectable before the seventh day after ovulation.[52] Between fertilization and implantation, substantial loss can occur. Therefore, hCG cannot be used as an indicator of fertilization, nor as an indicator of early embryo loss before implantation.[66]

The fertilization rates reported for the inert IUD (Table II) are somewhat lower than the sperm recovery rates (Table I) for most of the studies, and the CIs overlap, suggesting plausible concordance of the data. The single exception is the study of sperm recovery by El-Habashi et al,[37] which gives a rate of sperm recovery that is implausibly low in comparison to the fertilization rates. Although estimates for both sperm recovery and fertilization vary widely for the copper IUD, all CIs overlap, suggesting that, rather than conflicting data, there are insufficient data to determine more precisely the true rates of either sperm transport or fertilization. Although there are no sperm recovery data for the progestin IUD, the fertilization data suggest that the rates of sperm transport and fertilization for the lower-dose progestin IUDs are likely comparable to those for the inert IUD (Table II). It is important to note that these data do not include the higher-dose copper IUD (ie, the Copper-380 IUD), nor the higher-dose progestin IUD (ie, the Levonorgestrel-20 IUD).

Effects on the endometrium

It is well established that IUDs cause endometrial changes, with the type of changes present dependent on the type of IUD. Copper IUDs alter endometrial development little, but they do increase the number of leukocytes in the endometrium, indicating a chronic inflammatory response.[21] In addition, they alter the cellular metabo-

lism of the endometrium.[67] Progestin IUDs cause endometrial suppression with decreased thickness, size of the glands, and amount of secretions.[68, 69] Copper IUDs, the progesterone IUD, and the levonorgestrel IUD also alter cytokines and integrins in the endometrial lining, which would likely inhibit uterine implantation in the event that a blastocyst does reach the uterus.[70-72]

Effects on ectopic pregnancy

The percentage of clinically recognized pregnancies that are ectopic in users of inert and copper IUDs is about 3% to 4%, whereas for levonorgestrel and progesterone it is about 25%.[73,74] A number of studies suggest that inert and copper IUDs differentially reduce proximal tubal pregnancy and intrauterine pregnancy more than they reduce distal tubal and ovarian pregnancy.[75-78] These data support the existence of a postfertilization effect for the IUD but cannot be used to estimate its magnitude. The inflammatory state induced by the IUD in the endometrium probably extends to the fallopian tubes (especially with the copper IUD), where it may prevent tubal implantation and cause destruction of some fertilized ova that may otherwise have resulted in ectopic pregnancy.[3,5]

Levonorgestrel-20 IUD

The Levonorgestrel-20 IUD (Mirena; Schering AG Pharmaceutical, Germany), developed in 1980, has been used extensively in Europe and elsewhere. It has recently been approved for use in the United States. This IUD is highly effective to avoid clinical pregnancy, with a pregnancy rate around 0.1 per 100 woman-years. The levonorgestrel IUD has a minimal effect on the ovarian pituitary axis, and up to 85% of women are ovulatory during its use.[15] The rate of ovulation may increase with length of time that the device is worn.[24] The strongest biologic effect of this IUD is local suppression of the endometrium. Estrogen and progesterone receptors are depressed,[79] and morphologic and biochemical features of the endometrium indicate a profound suppression of endometrial function.[80-83] In addition, inflammation in the endometrium has been demonstrated to be similar to that of inert IUDs.[83] These endometrial effects result in decreased bleeding over time, and some women using the levonorgestrel IUD have amenorrhea. However, amenorrhea does not necessarily imply that ovulation is not occurring but that it is primarily due to the endometrial effects.[15] The epithelium and secretory activity of the tubal epithelium is also diminished by the levonorgestrel IUD,[83] which would suggest that the likelihood of tubal implantation may also be decreased. At the 20- g daily dose, the levonorgestrel IUD substantially lowers the absolute rate of ectopic pregnancy, but the proportion of pregnancies that are ectopic is as high as for the progestin IUD.[74] Cervical mucus favorable to the transport of sperm has been documented in the majority of ovulatory cycles during use of the levonorgestrel IUD.[22] Overall, the consensus has been that levonorgestrel IUDs, like progesterone IUDs, act primarily by suppressing the endometrium, an effect that is likely to prevent implantation.[12,84] However, endometrial effects may also result in the inhibition of sperm migration.

Estimating the contribution of postfertilization effects

There are insufficient data to elucidate the exact contribution of the individual mechanisms for the various IUDs. However, given that some data are available for fertilization rates and that we know the clinical pregnancy rates for the various IUDs, it is possible to estimate the collective contribution of the prefertilization effects and postfertilization effects. To accomplish this, we adapted the model originally described by Lehfeldt et al.[75]

The model is simply stated as follows:

$$(\text{Fertilization rate per cycle}) \cdot (1 - [\text{Conditional postfertilization loss rate per cycle}]) = \text{Clinical pregnancy rate per cycle}$$

In the equation, the conditional postfertilization loss rate per cycle refers only to cycles wherein fertilization has occurred. The term (1 – [Conditional postfertilization loss rate per cycle]) can also be referred to as the conditional rate of survival of the preimplantation embryo.

The fertilization rate per cycle gives a direct estimate of the contribution of prefertilization mechanisms (Table II). Clinical pregnancy rates per year are known and can be used to calculate clinical pregnancy rates per cycle, based on the formula:

$$1 - (1 - [\text{Yearly pregnancy rate}])^{(1/13)} = (\text{Per cycle pregnancy rate})$$

For example, for the inert IUD, a yearly pregnancy rate of 1.9 per 100 woman-years corresponds to a per cycle pregnancy rate of 1.46×10^{-3}.[74] By dividing the fertilization rate per cycle into the clinical pregnancy rate per cycle, we obtained an estimate of the conditional per cycle postfertilization survival rate in the presence of the IUD, which we subtracted from 1 to obtain the conditional per cycle rate of postfertilization loss.

We applied this model to the two modern IUDs that are considered most effective in preventing pregnancy, the Copper-380 IUD (Paragard T380 A; Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ) and the Levonorgestrel-20 IUD.[74,85-87] Although clinical pregnancy rates for these IUDs are well established, there has been no direct assessment of fertilization rates in these types of IUDs. However, fertilization rates of older forms of IUDs together with conservative assumptions can be used to estimate the fertilization rates for these two modern IUDs.

Table II. Evidence of fertilization during use of various IUDs and in control subjects

		Direct observation of fertilization of recovered ova		*Measurement of early pregnancy factor by rosette inhibition test*	
Type of IUD	*Study*	*No. of fertilized ova/ ova observed*	*Proportion of ova fertilized (95% CI)*	*No. of cases positive/cycles observed*	*Proportion of cycles positive (95% CI)*
No IUD (control)	Ortiz et al (1996)[3]*	14/18	0.77 (0.52-0.94)		
	Rolfe (1982)[50]			18/26	0.69 (0.48-0.86)
	Smart et al (1982)[63]			14/21	0.67 (0.43-0.85)
	Fan and Zheng (1997)[52]			35/70	0.50 (0.38-0.62)
Inert IUD	Ortiz et al (1996)[3]*	1/4	0.25 (0.01-0.81)		
	Clewe et al (1971)[49]	1/5	0.20 (0.01-0.72)		
	Smart (1982)[51]			4/8	0.5 (0.16-0.84)
Copper IUD	Ortiz et al (1996)[3]†	0/5	0.0 (0.0-0.52)		
	Smart et al (1982)[51]			2/12	0.17 (0.02-0.48)
Hormonal IUD	Ortiz et al (1996)[3]‡	1/5	0.20 (0.01-0.72)		

*The 1996 analysis of Ortiz et al is based on a reexamination of the ova originally recovered by Alvarez et al (1988),[48] using electron microscopy.

†For the copper IUD, Ortiz et al reexamined the ova recovered by Alvarez et al and reported that two of five ova were invaded by macrophages and had insufficient cytoplasm remaining either to confirm or exclude the occurrence of fertilization. If these two ova are assumed to be unfertilized, the low estimate is obtained, which is presented in the table. If these two ova are assumed to be fertilized, a high estimate is obtained of 2/5, or 0.40 (0.05-0.85).

‡Hormonal IUD results from the data from Alvarez et al (reanalyzed by Ortiz et al) include both progesterone and levonorgestrel (2 g) IUDs.

We used data for the inert IUD to establish a minimum benchmark for the magnitude of postfertilization effect of all IUDs because in the event of fertilization the medicated IUDs (copper or levonorgestrel) should be at least as effective in preventing a clinically recognized pregnancy (ie, their postfertilization effects should be at least as strong as for the inert IUD). We combined data from Alvarez et al (1988)[48] and Ortiz et al (1996)[3] with those from Clewe et al (1971)[49] (Table II) to estimate a maximum per cycle fertilization rate of 22.2%. We used an opportunity factor of 0.7 to account for the frequency and timing of intercourse, yielding a per cycle fertilization rate of 15.6%). (The opportunity factor is discussed further below.) Taken with a yearly clinical pregnancy rate of 1.9 per 100 women years,[74] this model informs us that 99.1% of all fertilized ova are lost in the presence of the inert IUD.

Neither Alvarez et al[48] nor Ortiz et al[3] observed fertilization in the presence of the copper IUD. However, their observation was based on only five ova, and two of them had been invaded by macrophages so that the exclusion of fertilization was not possible. As noted, Smart et al[51] found that EPF measurements suggested that fertilization occurred in 17% of cycles, but this study was done with older, lower-dose copper IUDs, which may have less spermicidal and ovicidal effect compared with the Copper-380. We therefore used a reverse estimation procedure for the Copper-380. Rather than using the fertilization rate and the pregnancy rate to estimate the postfertilization loss of fertilized ova, we used the clinical pregnancy rate and the postfertilization loss of ova to estimate the fertilization rate. To do this, we first assumed that the conditional rate of postfertilization loss would be the same as for the inert IUD. In actuality, the postfertilization loss with the copper IUD should be substantially higher than for the inert IUD because copper increases the inflammatory reaction in both the endometrium and the fallopian tube.[5,21] Therefore, this is a conservative assumption, corresponding to the loss of 99.1% of all fertilized ova in the presence of the Copper-380 IUD. A liberal assumption is that the conditional rate of survival of the preimplantation embryo is half of what it would be in the presence of the inert IUD, corresponding to the loss of 99.5% of all fertilized ova in the presence of the Copper-380 IUD. Together with a clinical pregnancy rate of 0.5 per 100 women-years,[85,88,89] these alternate assumptions yield estimated per cycle fertilization rates for the Copper-380 IUD of 4.1% and 8.1%, respectively.

We faced similar difficulties in estimating the fertilization rate for the Levonorgestrel-20 IUD because no direct data are available for this type of IUD. There is wide agreement that the copper IUDs (including the Copper-380) have a more pronounced spermicidal effect than do the progestin IUDs (including the Levonorgestrel-20). Therefore, a conservative assumption is to set the per cycle fertilization rate for the Levonorgestrel-20 to be the same as for the Copper-380 estimation described above, namely, 4.1%. The Levonorgestrel-20 IUD has been shown to have relatively little effect on ovulation and cervical mucus and allows good sperm penetration in ovulatory cycles.[22] Further, inflammation in the endometrium is actually significantly lower with the levonorgestrel 20 g IUD compared with the levonorgestrel 2 g IUD,[81] arguing against an increased spermicidal effect in the uterus relative to the older progestin IUDs. Therefore, a

reasonable scenario representing the upper limit of per-cycle fertilization of the Levonorgestrel-20 IUD is to set it equal to the fertilization rate found by Ortiz et al[3] (from Alvarez et al[48]). One fertilized ova of five recovered from progestin IUD users yields an estimated maximum 20.0% per cycle fertilization rate (Table II). Multiplying this by the opportunity factor of 0.7 yields an upper estimate of a 14.0% fertilization rate per cycle. With a clinical pregnancy rate of 0.1 per 100 women-years,[74,90] the Levonorgestrel-20 IUD is thus estimated to be associated with the loss of 99.9% to 99.95% of all fertilized ova.

The results of the calculations noted above are all summarized in Table III. For clinical interpretation, we used the postfertilization loss rates and fertilization rates to calculate an estimated number of postfertilization losses per woman per year, and these are reported in the fourth column of Table III.

A further issue in this estimation procedure is that the estimated rate of postfertilization loss includes natural loss that would have happened even without the IUD in place. To account for this natural loss, we applied a natural rate of postfertilization loss estimated from the available data. We used a maximum fertilization rate per cycle in the absence of the IUD of 0.77 (Table II),[48] and multiplied this by an opportunity factor of 0.7, to obtain an expected per cycle fertilization rate of 0.54 (54%). The opportunity factor represents the decrease in the opportunity to attain the maximal possible fertilization rate because of the frequency and timing of sexual intercourse. We next assume a natural per cycle rate of clinically identified pregnancy of 0.2, which is consistent with population-based studies that indicate a median time to pregnancy of 3 months and is consistent with recent studies that suggest a maximum possible per cycle pregnancy rate of 0.33 with completely optimized intercourse.[91,92] From these assumptions, we calculated a rate of natural postfertilization survival rate to clinically identified pregnancy of 0.367 (0.2/0.54), which is low, yet not inconsistent with estimates from other investigators.[50,61,93] We then inserted this as an additional term in the previous calculation to obtain a rate of postfertilization loss that is uniquely attributable to the IUD. Whether this natural loss is assumed to happen before or after the IUD-induced loss affects what proportion of the total postfertilization loss rate (which remains unchanged) is attributed to the IUD. If the natural loss is assumed to occur completely before the IUD-induced loss, then a lower-limit estimate for IUD-induced loss is obtained. If the natural loss is assumed to occur completely after the IUD-induced loss, then an upper-limit estimate for IUD-induced loss is obtained. These estimates are reported in the last two columns of Table III, in terms of numbers of postfertilization losses per women per year attributable to the IUD.

Physiologically, it is likely that the true rate of postfertilization loss attributable to the IUD is closer to the higher-limit estimate because the bulk of the evidence suggests that the postfertilization effects of the IUD occur at a very early stage of embryonic development. This evidence includes the higher rate of abnormal development of recovered fertilized ova in IUD users compared with women not using contraception,[3,48] the adverse tubal environment for development of the fertilized ova in IUD users compared with women not using contraception, and the virtual absence of hCG among IUD users in the more recent studies conducted with specific hCG assays.[3,64,66]

Relative contribution of postfertilization and prefertilization effects

Our estimation procedure quantitatively illustrates some important physiologic principles about the mechanisms of action of the IUD. Prefertilization mechanisms and postfertilization mechanisms do not operate simultaneously. Postfertilization mechanisms come into play only if prefertilization mechanisms do not prevent fertilization. Although prefertilization mechanisms operate in the majority of cycles, they are insufficient to attain the high efficacy of the IUD in preventing clinical pregnancy. As a hypothetic example, if there were absolutely no IUD-induced postfertilization effect, and if prefertilization effects were to limit fertilizations to 1% of cycles for a given type of IUD, the clinical pregnancy rate per 100 woman-years would be 4.7%, even considering an estimated natural postfertilization survival rate of 36.7%, as we have done in these models. Therefore, it is necessary for the postfertilization mechanism to be extremely effective (>99%) to account for the known very low clinical pregnancy rates of the IUD (Table III). This highly effective mechanism is operative only in the minority of cycles in which fertilization has occurred. Yet in the course of a year, this results in a conservative estimate of 0.2 to 1.0 postfertilization losses per woman per year caused by the IUD. As another hypothetic example, if one were again to assume that there was no IUD-induced postfertilization loss, and again that the estimated natural postfertilization survival rate of 36.7%, then to achieve a clinical yearly pregnancy rate of 0.1 per 100 woman-years, the per cycle fertilization rate would need to be 0.03%, which defies biologic credibility and is not consistent with available data on sperm transport and fertilization rates in the presence of the IUD.

Comment

On the basis of currently available rates of fertilization in the presence of various types of IUD and the known clinical pregnancy rates for each type of IUD, we have calculated expected conditional rates of postfertilization loss for each type of IUD. Further, with use of currently available rates of fertilization and clinical pregnancy for

Table III. Model parameters and estimates of postfertilization loss during use of various IUDs

IUD scenario	*Clinical pregnancy rate/100 woman-y*	*Fertilization rate/ cycle (%)*	*Estimated postfertilization losses (% of all fertilized ova)*	*Estimated No. of postfertilization losses/woman/y*		
				Total No.	*No. attributable to IUD, low estimate*	*No. attributable to IUD, high estimate*
Baseline (inert IUD)*	1.9	15.6	99.1	2.00	0.72	1.97
Copper-380 IUD†	0.5	4.1	99.1	0.52	0.19	0.51
Copper-380 IUD‡	0.5	8.1	99.5	1.05	0.38	1.04
Levonorgestrel-20 IUD§	0.1	4.1	99.8	0.53	0.19	0.53
Levonorgestrel-20 IUD‖	0.1	14.0	99.95	1.82	0.67	1.82

*The fertilization rate for the baseline scenario (inert IUD) is based on the combined data of Ortiz et al (1996),[3] Alvarez (1988),[48] and Clewe (1971),[49] as outlined in Table II. Two fertilized ova of nine recovered yields of an estimated maximum 22.2% per cycle fertilization rate. This is multiplied by a factor of 0.7 to account for the frequency and timing of intercourse, yielding an estimated 15.6% fertilization rate per cycle.

†This scenario conservatively constrains the rate of postfertilization loss with the Copper-380 IUD to be equal to that of the inert IUD.

‡For this scenario, the survival rate of the preimplantation embryo is set at 0.47%, half the rate of 0.95% for the inert IUD.

§For the first Levonorgestrel-20 scenario, the fertilization rate per cycle is conservatively constrained to be equal to that of the conservative Copper-380 IUD scenario.

‖For the second Levonorgestrel-20 scenario, the fertilization rate per cycle is set by the data of Ortiz (1996),[3] from Alvarez (1988),[48] as outlined in Table II. One fertilized ova of five recovered from progestin IUD users yields an estimated maximum 20.0% per cycle fertilization rate. This is multiplied by a factor of 0.7 to account for the frequency and timing of intercourse, yielding an estimated 14.0% fertilization rate per cycle.

couples using no contraception, we have estimated yearly rates of postfertilization loss attributable to various IUDs (Table III). Our model is limited by the paucity of direct data for the occurrence of fertilization in the presence of the IUD. In particular, there are no direct data for the Copper-380 IUD or the Levonorgestrel-20 IUD. Therefore, our estimates must not be regarded as definitive or precise. However, our model is based on and is consistent with known reproductive physiology and all available data regarding the mechanism of action of all types of IUDs. Further, the assumptions we have made in extrapolating from one type of IUD to the other are all quite conservative, for the reasons we have outlined previously. If anything, we believe that the estimates for numbers of postfertilization losses given in Table III are likely to be low. We hope that in the future more accurate means of detection of fertilization in vivo will allow for improved estimates of the prefertilization and postfertilization effects of the IUD.

Regardless of the exact magnitude of the postfertilization effect of IUDs, our model illustrates that, for the IUD to achieve its effectiveness in preventing clinical pregnancy, it must have a very strong conditional postfertilization effect, even if its predominant effect is to inhibit fertilization. In other words, even if fertilization occurs relatively infrequently, a very potent postfertilization effect is required to achieve the observed low rates of clinical pregnancy. In previous debates on the mechanism of action of the IUD, there was some discussion as to whether postfertilization effects were a "major" or "main" effect of the IUD.[9,94-96] Our model illustrates clearly that, although the majority of pregnancy prevention occurs before fertilization, postfertilization effects make substantial and essential contributions to the effectiveness of all types of IUDs.

With regard to the postfertilization effect of the IUD, it is likely that the majority of this effect occurs before the embryo enters the uterus. As discussed, the low recovery of ova from the uterus in IUD users, as well as the lack of hCG rise in more recent studies of IUD users, suggest that the major postfertilization effect is destruction of the early embryo in the fallopian tube, in the same way that the major prefertilization effect is likely to be destruction of sperm and ova. For the copper IUD, this embryocidal effect may be more a result of inflammation and direct toxicity, whereas with the progestin IUDs it may result more from inhibition of transport through the fallopian tube, along with prevention of implantation, preventing long-term viability of the embryo.[83,97,98]

A limitation of our model is that it does not account for underlying heterogeneity in the fertility of couples, which can be substantial.[99] In other words, our calculations implicitly assume that the underlying potential for pregnancy is the same among couples in each of the IUD effectiveness studies and in each of the fertilization studies. Still, our estimates are based on the best available data in each case, and there is no reason to suspect that couples with infertility had been disproportionately included in any of the studies.

We believe that these results have important implications for the counseling of women and couples who are considering the use of the IUD. Because our estimates are based on the best evidence currently available, we suggest that they could be used in clinical counseling for women who may object to postfertilization effects.[16,17] In

Table III, the high estimates of yearly postfertilization losses attributable to the IUD do not assume higher rates of fertilization; rather, they assume that the bulk of the postfertilization effect occurs before the natural loss of embryos around the time of implantation. In contrast, the low estimates in Table III assume that all natural postfertilization loss would have occurred anyway and that only additional loss may be attributed to the IUD. Both estimates are based on an estimated low rate of natural postfertilization survival to clinical pregnancy (36.7%); if the natural postfertilization survival rate is higher, then all estimates of postfertilization losses attributable to the IUD would be higher also.

In conclusion, a rigorous examination of the evidence on the mechanism of action of IUDs indicates that both prefertilization and postfertilization effects are significant contributors to the clinical efficacy of all types of IUDs. Although prefertilization effects are more prominent for the copper IUD, both prefertilization and postfertilization mechanisms of action contribute significantly to the effectiveness of all types of intrauterine devices. Patients considering use of the IUD should be made aware of the available data about its mechanisms of action.

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