ORIGINAL ARTICLE

Observational series on women using the contraceptive Mirena® concurrently with anti-epileptic and other enzyme-inducing drugs

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(Accepted 8th February 2002)

The Journal of Family Planning and Reproductive Health Care 2002: **28(2)**: 78-80

Abstract

Context. *Contraception for women on enzyme-inducing drugs.*

Objective. *To gather preliminary information on the contraceptive efficacy of the hormone-releasing intrauterine system (IUS) Mirena®, when used concurrently with enzyme-inducers.*

Design. *Observational series.*

Setting/participants. *Mirena® users on enzyme-inducers were recruited from within the Margaret Pyke Centre and via doctors from throughout the UK. Data were collected systematically on structured questionnaires with particular reference to duration of Mirena® use, exposure to pregnancy risk, type of concurrent medication, and reasons for drop-out.*

Main outcome measure. *Accidental pregnancies.*

Results. *To date, 56 women have provided follow-up information. Most took enzyme-inducers for epilepsy. They have accumulated 1454 months of use, of which 1075 months represent exposure to pregnancy risk. Only one apparently true Mirena® failure has been documented, representing a failure rate of 1.1 per 100 woman-years (95% CI 0.03–6.25). Including a second pregnancy, probably conceived after the Mirena® had been removed, would raise the failure rate to 2.2 per 100 woman-years (95% CI 0.27–8.07). Although 9/30 Mirena® removals were followed by re-insertion, only the first segment of use is analysed.*

Conclusion. *As this is a pilot study, no firm conclusions can be drawn, but our preliminary results suggest that any increased pregnancy risk, if it exists, falls within acceptable bounds.*

Key message points

- Oral hormonal contraceptives and implants, when taken concurrently with enzyme-inducing drugs, carry the risk of drug interaction and hence reduced efficacy.
- Not all anticonvulsants are enzyme-inducers.
- Though in theory drug interaction between Mirena® and enzyme-inducers is possible, contraceptive protection from the local mechanisms is unlikely to be reduced by enzyme-inducers acting on the liver.
- Since only one apparently true Mirena® failure occurred in our study, any increased pregnancy risk, if it exists, falls within acceptable bounds.
- Given the teratogenic potential of anti-epileptic drugs, we consider Mirena® as a first-line method for women on enzyme-inducers.

Introduction

Finding an acceptable and effective method of contraception is problematic for many women, even more so for those taking concurrent enzyme-inducing medication. This group presents a particular challenge and can also be the cause of confusion among prescribers in this situation where a high degree of contraceptive protection is often a key requirement. Copper intrauterine contraceptive devices (IUDs) may be inappropriate if there is a history of menorrhagia, barrier methods may not be acceptable to either or both partners, and oral contraceptives (OCs) carry the risk of drug interactions and hence reduced efficacy,[1] though not all anticonvulsants are enzyme-inducers.[2,3] In the presence of enzyme-inducers, even increasing the oestrogen dose in combined OCs, tri-cycling, and/or decreasing the pill-free interval give no guarantee of protection, though such measures may reduce the risk of accidental pregnancies. Comparative data on OC efficacy in women taking enzyme-inducers versus those not taking such medication are sparse, though numerous anecdotal reports suggest a higher risk in the former.[4–7] Surveys of healthcare professionals[8] and women suffering from epilepsy[9] have clearly demonstrated the need for better information, particularly with regard to the risk of drug interactions.

A possibly more suitable option for women on enzyme-inducers might be the hormone-releasing intrauterine system (IUS) Mirena®. This can be true even for nulliparous women, with appropriate counselling and skilled insertion. The IUS has various modes of action: thickening of the cervical mucus and local inflammatory effects in the uterine cavity impairs sperm migration through the uterus; ovulation is inhibited to various degrees during treatment time in 25–55% of women; and the endometrium is suppressed.

In women not taking enzyme-inducers Mirena® is a highly effective contraceptive with a failure rate of only two pregnancies per 1000 women per year. Whether this exceptionally high level of efficacy also applies to women on enzyme-inducers is at present unknown. In theory, drug interaction is not impossible since some of the progestogen released enters the general circulation. Conversely, there is direct local release leading to high levonorgestrel concentrations in the endometrium and the utero-tubo-cervical fluid, hence contraceptive protection from the local mechanisms is unlikely to be reduced by enzyme-inducers acting at the liver.

In view of the continuing uncertainty, some prescribers might be unnecessarily cautious and deprive women on enzyme-inducers of a potential useful method.

Enquiries to the Committee on Safety of Medicines (CSM) showed that, by mid-March 2001, only two cases of unintended pregnancy in Mirena® users associated with anticonvulsant therapy had been reported via the Yellow Card Scheme (CSM, personal communication). Subsequent enquiries by one of the authors (WB) strongly suggest that one of the two cases was identical with Patient Ms C (see later) and probably was never pregnant. This was not apparent at the time the case was reported to the CSM.

To address this important aspect, the authors established a database in 1996 which, to date, has accumulated records on 56 patients. The report below is the first publication on the experience of a cohort of IUS users on concurrent enzyme-inducers.

Setting/participants

The survey was publicised by word of mouth and via mention in the *British Journal of Family Planning*.[10] Data were collected via the local clinic doctor or via direct postal/telephone contact with patients on structured questionnaires. The following were recorded: the woman's age at IUS insertion; date of insertion; details of enzyme-inducers taken; whether and for how long the IUS was relied upon for contraception (rather than used merely to achieve/maintain reduced menstrual bleeding); changes in drugs prescribed; and, if so, whether switching medication was accompanied by alterations in menstrual bleeding patterns; details of bleeding patterns; and date and reasons for IUS removal. For logistical reasons, follow-up information was sent to the authors as and when it became available, at approximately annual intervals, rather than at predetermined points after the IUS insertion. The cut-off date for data analysis was set at 31 December 2000. All patients not known to have withdrawn from the survey prior to that date were sent a follow-up questionnaire in January 2001 in order to determine whether they were still using the Mirena®.

Our primary interest was the documentation of contraceptive effectiveness, based on accidental pregnancies, calculated by Pearl Index (PI). Confidence intervals for the PI were calculated by assuming that the number of pregnancies followed a Poisson distribution and by inversion of the exact significance test. Menstrual bleeding data were also collected as a possible surrogate marker for drug interaction.

Results

To date, 65 patients have been recruited. Of these, nine are excluded from this report because in eight the IUS fittings took place only recently and follow-up data are not yet available and one woman failed to return to her clinic after the insertion. The majority of patients were on a combination of drugs, of which at least one is known to be an enzyme-inducer. Epilepsy was the main indication, though seven women were taking enzyme-inducers for other reasons (Table 1). Six women were on treatments which, to date, did not include any enzyme-inducers (Table 2), and they are excluded from the efficacy analysis, as are the three women who, for a variety of reasons, were never at risk of pregnancy. In addition, segments of use during which the woman temporarily used additional contraceptives, were not sexually active for more than one month, or temporarily used non-enzyme-inducers, were also excluded from the efficacy calculations. In cases of accidental pregnancy, efforts were made to establish the precise circumstances surrounding conception.

Table 1 *Indications for medications prescribed (including non-enzyme-inducers)*

Indications	Patients (n = 56) (%)
Epilepsy	49 (87.5)
HIV/AIDS	3 (5.3)
Multiple sclerosis	2 (3.6)
Depression	1 (1.8)
Brain tumour	1 (1.8)

Table 2 *Medications taken by survey population*[a]

Enzyme-inducers	Non-enzyme-inducers
Carbamazepine	Amitriptyline
Efavirenz	Carbimazole
Nevirapine	Clobazam
Phenytoin	Combivir
Phenobarbitone	Diclofenac
Primidone	Gabapentin
Rifabutin	Lamotrigine
Ritonavir	Lithium citrate
Topiramate	Nefopam
	Sodium valproate
	Trimipramine
	Vigabatrin

[a]Many patients were on a combination of drugs and/or switched medication during the period of observation.

First segment results

Overall results are presented in Table 3. Fifty-six women used the IUS for a total of 1454 months. The main indication was contraception, though three used it successfully solely for treatment of menorrhagia. Two women were withdrawn on account of having moved away, and 30 had their IUS removed for reasons listed in Table 4. Nine of the 30 patients elected to have a second IUS (Table 5).

Accidental pregnancies

Two accidental pregnancies were reported during 1075 months of exposure, of which one appears to be a true Mirena® failure, while the second case (ectopic) was most probably conceived just after the IUS was removed. This represents a failure rate of 1.1 per 100 woman-years (95% CI 0.03–6.25), or 2.2 per 100 woman-years (95% CI 0.27–8.07) if the second pregnancy is included. Brief case histories follow.

Case 1 (Ms A). This 42-year-old patient had used the IUS for nearly 24 months before she conceived. She was on primidone 500 mg and phenytoin 300 mg daily. She elected to have the pregnancy terminated. Clinical examination excluded expulsion (partial or complete) and the IUS was removed. Ultrasound scan performed 6 weeks later to exclude uterine pathology showed the uterus to be normal

Table 3 *Results: First segment use*

Parameter	n
Women in overall analysis	56
Mean age in years (SD)	32 (7.4)
Age range in years	17–49
Total months of use	1454
Median months of use	24
Range of months of use	1–71
Women in *efficacy* analysis	47
Total months of use *for contraception*	1075
Median months of use *for contraception*	21
Range of months of use *for contraception*	1–60
Women withdrawn	32

SD, Standard deviation.

Table 4 *Reasons for withdrawal*[a]

Reason	n	(%)
Total number of withdrawals	32	(57)
Accidental pregnancy[b]	2	(3.6)
Planned pregnancy	7	(12.5)
IUS expired	5	(8.9)
Perforation	1	(1.8)
Medical reasons possibly related to IUS[c]	12	(21.4)
Medical reasons unrelated to IUS	3	(5.3)
Moved away	2	(3.6)

IUS, Intrauterine system.
[a]The percentage values are based on total number of women in the study.
[b]Includes one apparently true Mirena® failure.
[c]Includes three women with a past history of heavy/prolonged menstrual bleeding in whom the IUS was unsuccessful in controlling the bleeding, including one on warfarin who requested IUS removal after only 1 month.

Table 5 *Results: Second segment use*

Parameter	n
Women in overall analysis	9
Total months of use	127
Median months of use	11
Range of months of use	1–38
Total months of use *for contraception*	66
Median months of use *for contraception*	9
Range of months of use *for contraception*	1–29
Accidental pregnancies	0
Women withdrawn	0

in size and shape with no fibroids seen, nor were any submucous fibroids or polyps demonstrated.

Case 2 (Ms B). A patient in her early 30s with a history of endometriosis, chronic pelvic pain, and irregular vaginal bleeding had a Norplant removed and a Mirena® inserted at the same time in early 1997. She was on phenytoin for epilepsy, though the precise dosage is unknown. Four months later, the Mirena® was removed at the patient's request on account of dyspareunia and the string of the IUS causing discomfort to her partner. As intercourse had taken place 42 hours prior to the IUS removal, she was also supplied with emergency contraception (oestrogen/progestogen regimen PC4). Five days after the removal she was prescribed Orthonovin 1/50. Her last menstrual period was 17 days before the Mirena® was removed, aside from some light erratic bleeding. She was admitted to hospital with a history of severe lower abdominal pain and vaginal bleeding 33 days after the removal of the Mirena®. A pregnancy test was positive and laparotomy revealed a ruptured ectopic pregnancy. The patient made an uneventful recovery. Since the IUS was removed only 42 hours after intercourse, when there might still have been live sperm present, and the Pill was not prescribed until 5 days after removal, it is more likely that conception occurred during this critical non-protected time gap, despite emergency contraception, rather than as a result of Mirena® failure.

A further patient (Ms C), not included among the accidental pregnancies, had used the Mirena® successfully for 18 months. The Mirena® was then removed on the initiative of a locum physician on account of amenorrhoea of 17 months duration and nausea. The patient was on carbamazepine, later changed to phenytoin. One month after IUS removal, the woman attended her local hospital with a 1 day history of 'heavy bleeding', which was erroneously (and with no supporting data) diagnosed as a miscarriage. Subsequent investigations by one of the authors (WB) revealed that the patient was probably never pregnant, and that the patient and the hospital staff misinterpreted her first spontaneous menstrual period 4 weeks after the IUS removal (and after 17 months amenorrhoea) to be a miscarriage. The above cases demonstrate the importance of:

(1) Not removing an IUS on account of amenorrhoea, unless medical circumstances dictate otherwise.

(2) Ensuring that effective alternative contraception is adopted as soon as the IUS is removed or even earlier.

(3) Elucidating the precise circumstances surrounding conception before a case is judged to be a Mirena® failure.

Discussion

This preliminary report, based on 56 patients, can provide only tentative data. The observed failure rate of 1.1 per 100 woman-years, based on the one apparently true Mirena® failure, though higher than the rate of 0.2 per 100 women-years for Mirena® users not taking enzyme-inducers, compares favourably with rates reported for women on OCs and enzyme-inducers, and better than for barrier methods. Not surprisingly, owing to the paucity of our data, the confidence intervals are wide. Ideally, a much larger study with a comparison group of Mirena® users not on enzyme-inducers should be undertaken. Given Mirena®'s primarily local contraceptive effects, we consider it probable that such a study would confirm our findings of an acceptable failure rate. Furthermore, the infrequency of irregular bleeding in our patients is compatible with the absence of a marked effect of the enzyme-inducers on the local action of Mirena®. However, since the IUS can produce menstrual irregularities, regardless of therapies, this requires further investigation. The authors hope to expand their database and would welcome contributions to it from anyone whose Mirena® patients are taking enzyme-inducers for whatever reason.

Pregnancy carries additional risks for women on enzyme-inducers, especially to the fetus. Hence, effective contraception is particularly important and, pending more data, we consider the IUS as a first-line method.

Conclusion

As this is a pilot study, no firm conclusions can be drawn, but our preliminary results suggest that any increased pregnancy risk, if it exists, falls within acceptable bounds.

Acknowledgements

We thank the Margaret Pyke Memorial Trust for having funded this survey; the doctors, nurses, and patients who contributed data for their much-valued help; and Professor Stephen Senn for statistical advice.

Statements on funding and competing interests

Funding. The Margaret Pyke Memorial Trust has received research grants and John Guillebaud has received fees for lectures and short term consultancy arrangements from Leiras/Schering.

Competing interests. None declared.

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