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Mifepristone in South Australia

The first 1343 tablets

Background

Mifepristone has recently become available in Australia but its use is restricted.

Objective

To describe the use of mifepristone in South Australia in the period 2009–2010 and to explore options that may become available to general practitioners.

Discussion

Mifepristone has been added to regimens for early and second trimester abortions – both medical and surgical abortions. It has been most commonly used in early medical abortions. In this audit the complication rates of early medical abortion with mifepristone compared favourably to early surgical abortion. There are implications in service delivery of early medical abortion compared to early surgical abortion.

Keywords: abortion, induced; mifepristone; misoprostol

completed the steps required to obtain a licence to market mifepristone in Australia.

One avenue for medical practitioners to access an unlicensed drug is to gain the support of a Human Research Ethics Committee (constituted according to National Health and Medical Research Council guidelines) and then to apply to the TGA under the Authorised Prescriber scheme.⁴ A group of South Australian medical practitioners sought authorisation to prescribe mifepristone for induction of first and second trimester medical abortion and for cervical priming before first and second trimester surgical abortion. Approval was granted in 2008 and supplies arrived in February 2009. Details of regimens for mifepristone use in South Australia are shown in *Table 1*. Since then, mifepristone has been gradually introduced into routine abortion care.

Method

Outcomes following medical and surgical abortions in five metropolitan public clinics and medical abortions conducted in two obstetric units were reviewed following approval from three Human Research Ethics Committees. Data sets comprised all women who had medical or surgical abortions up to 9 weeks gestation in the largest clinic and all those who had first trimester medical or surgical abortions in four smaller clinics during the period 1 January 2009 to 31 December 2010. In addition, the records of all women who were prescribed mifepristone for second trimester medical abortion or cervical priming before second trimester surgical abortion in the same period were reviewed.

Outcome data was gathered by interrogation of an electronic clinical data repository (OACIS) containing records generated by the eight metropolitan public hospitals. Where an encounter with the public health system within 28 days of abortion was recorded, the diagnosis, pathology and radiology reports and discharge

The progesterone antagonist mifepristone has been in use for so long that the patent (RU486, by which it was known) has expired. After extensive use in many countries, including France (since 1988), China (since 1988), the United Kingdom (since 1991), the United States of America (since 2000) and New Zealand (since 2001), there is now ample evidence of its safety and efficacy in inducing abortion.¹ It also shows promise when used for a number of other indications including cervical ripening before surgical abortion, induction of labour at term, menstrual regulation, postcoital contraception and treatment of fibroids.²

The arrival of mifepristone in Australia was controversial.³ Use is regulated by the Therapeutic Goods Administration (TGA), however it remains an unlicensed drug as no company has yet

summary were reviewed. In addition, paper records were reviewed in every case where mifepristone had been prescribed.

Nine hundred and forty-seven mifepristone tablets were prescribed for early medical abortion, 321 for preoperative preparation before early surgical abortion (dilation and curettage of uterus [D&C]), 49 for second trimester medical abortion and 26 for preoperative preparation before second trimester surgical abortion (dilation and evacuation [D&E]) procedures in the first 24 months of routine use.

Results

There were 5823 early surgical and 947 early medical abortions conducted in the five centres in 24 months. In addition, there were 26 second trimester surgical abortions using mifepristone and 49 second trimester medical abortions conducted using mifepristone.

Adverse outcomes following first trimester abortion

Table 2 shows the complications in the 28 days following first trimester abortion. More than 1 in 50 women presented to an emergency department with gynaecological symptoms, most often

bleeding and/or pelvic pain; 1 in 100 was admitted for treatment of an abortion related problem (most often retained products of conception) and some of these were treated with D&C surgery.

The likelihood of being admitted for treatment of complications and of having D&C surgery to remove retained products of conception were both significantly ($p < 0.001$) higher following early medical abortion than they were following early surgical abortion.

Complications following first trimester abortion

Table 3 shows the serious complications following first trimester abortion including surgical injury, significant blood loss (>1000 mL with or without transfusion), treatment failure (continuing pregnancy after abortion) and systemic sepsis (with admission for intravenous antibiotic treatment). These were all rare events within 28 days of first trimester medical or surgical abortions.

Cervical preparation with mifepristone before surgical abortion

Among 5823 women who had first trimester surgical abortions with misoprostol as a cervical

priming agent, 321 were also treated with mifepristone preoperatively. In the following 28 days, five of these women (1.6%) presented to emergency departments with gynaecological symptoms. One was admitted for treatment of a uterine perforation.

Twenty-six women were treated with mifepristone in addition to misoprostol and/or osmotic dilation before second trimester surgical abortion (D&E). There were four (15%) cervical tears.

Experience and complications of second trimester medical abortion

Mifepristone was given before misoprostol for second trimester medical abortion in 49 cases. The delay from induction to delivery varied from 3 hours to over 55 hours. The mean time from misoprostol (or other oxytocic) administration to delivery was 17 hours and the median was 10 hours.

Two cases progressed to surgical D&E, one due to failure of the cervix to dilate and one due to maternal distress. Ten cases required manual removal of the placenta and prophylactic antibiotics. There were two postpartum haemorrhages. One required transfusion and overnight intensive care admission. One woman had high vaginal culture which was positive for *Streptococcus pneumoniae*, and was treated with intravenous and subsequently oral antibiotics. This was the only objectively proven infection in the series. Five others presented with symptoms of retained products of conception. Four of these were treated surgically (D&C). These complications are shown in Table 4.

Discussion

The rate of any adverse outcome following early abortion is low. Large numbers are required to demonstrate any difference in the frequency of these infrequent events between different treatment groups. This audit only captured care provided in public hospitals and not complications treated by general practitioners. The power of this audit was not sufficient to demonstrate any significant advantage in adding preoperative mifepristone to standard cervical priming with misoprostol before early surgical abortion and little can be made of the likelihood of the most

Table 1. Regimens for mifepristone use

Early medical abortion up to 63 days gestation

Mifepristone 200 mg oral followed by misoprostol 800 µg per vagina, sublingual or buccal after 0–72 hours. Further doses 200 µg misoprostol per vagina, sublingual or buccal three times per day on subsequent 2 days if cramping or heavy bleeding persist

Second trimester medical abortion

Mifepristone 200 mg oral followed by admission for induction of labour 0–72 hours later with 800 µg misoprostol per vagina and up to four further doses of 400 µg every 3 hours

Cervical priming before surgical abortion

Mifepristone 200 mg oral, hours or days before admission for surgery

Table 2. Common complications of first trimester abortion

Type of abortion	Emergency department presentation	Admission	Dilation and curettage
Surgical abortion with misoprostol +/- mifepristone priming	131/5823 (2.2%)	23/5823 (0.4%)	12/5823 (0.2%)
Early medical abortion	31/947 (3.3%)	54/947 (5.7%)	53/947 (5.6%)
First trimester abortions (medical + surgical)	162/6770 (2.4%)	77/6770 (1.1%)	65/6770 (1.0%)

Table 3. Serious complications of first trimester abortion

Type of abortion	Haemorrhage >1000 mL (ratio)	Treatment failure (ratio)	Admission for sepsis (ratio)	Surgical injury (ratio)
Surgical abortion with misoprostol +/- mifepristone priming	2/5823 1:3000	7/5823 1:850	4/5823 1:1500	4/5823 1:1500
Early medical abortion	4/947 1:200	1/947 1:950	2/947 1:480	–
First trimester abortions (medical + surgical)	6/6770 1:1000	8/6770 1:850	6/6670 1:1000	–

Table 4. Complications of second trimester medical abortion

Complication	Incidence	Rate
Any surgical intervention	16	33%
• dilation and curettage for retained products of conception	5	10%
• manual removal of placenta	10	20%
• failed induction requiring dilation and evacuation	2	4%
Retained products of conception	6	12%
Emergency department presentation	7	14%
Unplanned readmission	6	12%
Intensive care unit admission	1	2%
Microbiologically confirmed infection	1	2%
Significant haemorrhage >1000 mL +/- transfusion	2	4%

serious adverse outcomes of early abortion except to note that they are rare.

Comparison between the outcomes of early medical and surgical abortion has been made, however, the groups differ in that early medical abortion was only offered to women at less than 9 weeks gestation while women who had surgery included those with gestation up to 12 weeks. Women self selected medical abortion and factors such as previous obstetric experience are probably associated with willingness to undertake this procedure. Despite these confounding factors, the findings that women were more likely to be admitted and to have D&C surgery after early medical abortion than they were after early surgical abortion are consistent with the results reported in one much larger⁵ and one more tightly controlled series.⁶

Relatively few abortions are conducted in the second trimester. In South Australia only 7% of abortions are performed after 14 weeks and less than 2% after 20 weeks gestation.⁷ With small cohorts, it was difficult to assess the significance of complication rates. Complications were more

frequent than with first trimester abortion. Cervical tears were prominent among later surgical abortions conducted with mifepristone as a cervical priming agent, while placental retention requiring manual removal was particular to later medical abortion.

Following midtrimester medical abortion, emergency department presentation and subsequent admission were frequent. Manual removal of placenta and the high rate of unplanned surgical intervention (rate of 32%) in these cases imposes additional costs as well as placing demand on operating theatre resources. However, medical termination for fetal abnormality may enable fetal examination which could convey valuable information for ongoing care and counselling that primary surgical termination may not.⁸ The significant maternal and fetal risks of continuing a pregnancy where genetic termination is offered must be weighed against the complications of termination.

While the rates of unplanned surgical intervention in the South Australian cohort are high, they are similar to the rates described in

other centres and are comparable to medical terminations using only misoprostol.⁹ In addition, mifepristone administered 24–48 hours before misoprostol is known to reduce the rate of failed medical abortion,¹⁰ while use of a shorter interval between mifepristone and misoprostol doses may reduce time to delivery, as can other factors such as parity and lesser gestation.⁹ While the unplanned intervention rate in South Australia parallels other Australasian findings, the series was too small to be able to draw conclusions, in particular when commenting on induction times, which are multifactorial.

Adjustments on existing abortion services

Adopting mifepristone has various impacts on existing abortion services. Women are encouraged to present early for early medical abortion. They may present very early, with a pregnancy of unknown location. Transvaginal ultrasound and serial beta human chorionic gonadotrophin estimations are employed more frequently in clinics offering this option, as clinicians seek to identify ectopic pregnancies.

Women selecting early medical abortion are expected to manage pain, bleeding and nausea at home with the support of another adult. More time is required to prepare these women, and to engage them in the care process than is the case before surgical abortion; longer appointments are required.

As women (and referring GPs) become more familiar with early medical abortion, the number of women selecting this option has risen from 276 in 2009 to 539 in 2010. Doctors spend more time talking to patients in the clinic and less time in the operating theatre as more medical and fewer surgical abortions are conducted.

When used as a cervical priming agent, mifepristone occasionally results in abortion while awaiting surgery. While this is a safe outcome, it can cause anxiety. Surgery may need to be expedited.

Australian GPs and early medical abortion

Medical practitioners willing to undertake the process required to gain access to mifepristone have been obstetricians in tertiary referral centres and GPs providing abortion in specialised

clinics. General practitioners and specialists in private practice may have been precluded from using mifepristone by lack of access to an ethics committee or they may have been dissuaded by the application process.

If a company gains a licence to market mifepristone in Australia, prescribing will become less difficult. General practitioners will continue to be restrained from providing early medical abortion in jurisdictions where legislation requires abortion to be provided in hospitals (Northern Territory, South Australia and the Australian Capital Territory). If access to mifepristone becomes more straightforward, GPs in Victoria, Queensland, New South Wales, Western Australia and Tasmania will be able to consider providing early medical abortion. General practitioners who already diagnose pregnancies and who manage other problems in early pregnancy may then wish to include early medical abortion among the services they provide.

Important points

- Given a choice, some women prefer early medical abortion to a surgical procedure (D&C).
- Gaining access to mifepristone is difficult for GPs, but it may become more straightforward in the future.
- Both surgical and medical abortion are safe and effective, however, retained products of conception treated with D&C are more likely after early medical abortion.
- Complications become more frequent for both medical and surgical abortion as pregnancy progresses into the second trimester.

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