

CASE REPORT



Progesterone for preventing pregnancy termination after initiation of medical abortion with mifepristone

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ABSTRACT

Introduction: Abortion is often a difficult and traumatic decision for a woman to make. Perhaps greater distress occurs when a woman commences a medical abortion but then changes her mind and wishes to keep the now-threatened pregnancy. One published case series detailed a potential method to counter/reverse the abortifacient effect of mifepristone by administering parenteral progesterone in such situations.

Objectives: The present report details cases of women in similar circumstances who have been treated with progesterone. The aims were to document occurrences of where women have changed their mind after commencing medical abortion, as well as to explore some of the controversies and clinical issues surrounding their circumstances.

Methods: Women who had commenced medical abortion by ingesting mifepristone but who had not taken misoprostol independently contacted a national pregnancy support service the same day. Those meeting criteria for treatment received progesterone pessaries per vaginum for two weeks.

Results: Cases: 28-year-old woman, 6 weeks plus 1 day gestation; 35-year-old woman, 8 weeks plus 5 days gestation; and 27-year-old woman, 7 weeks plus 3 days gestation. Outcomes respectively were: healthy male baby delivered at 39 weeks gestation; healthy male baby delivered at term; and completed medical abortion.

Conclusions: Women have changed their mind after commencing medical abortion. Progesterone use in early pregnancy is low risk and its application to counter the effects of mifepristone in such circumstances may be clinically beneficial in preserving her threatened pregnancy. Further research is required, however, to provide definitive evidence.

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Introduction

Medical abortion using mifepristone and misoprostol has been registered for use in Australia up to 63 days gestation [1]. Abortion is one of the most common gynaecologic procedures performed in Australia [2] with an estimated 80,000 being performed each year [3]. One recent multi-centre study reported on 15,000 women who underwent early medical abortion between March 2013 and September 2015 [4]. Results were consistent with international experience in demonstrating a high abortion success rate (complete abortion not requiring surgical intervention) of greater than 95%. This figure did not, however, account for the approximately 13% of women who were lost to follow-up, which was significantly greater in rural and remote areas. This is important from a safety perspective, but also highlights potential deficits in continuity of care by the treating practitioner. Reasons for lack of follow-up were postulated and included time and financial costs associated with rural or remote location [4]. Current recommendations are for access to 24-h clinical and emergency surgical support until the abortion is complete [5].

Issues recounted by women after undertaking abortion include being pressured by others (37–64%), being unsure about the decision at the time (38–54%), needing more

time to make the decision (33–52%) and not being counselled on alternatives (45–79%) [6]. Figures for women being coerced to undergo termination of pregnancy are likely to be under-reported due to fear of being turned away from abortion services if the issue is raised [7]. Consequently, a proportion of women commencing the medical abortion regimen may change their mind before completing the drug course.

Progesterone is secreted by the corpus luteum and provides essential early pregnancy support in the luteal phase and first trimester until placental progesterone production begins. Low levels of circulating progesterone have been associated with early miscarriage [8] and there is increasing evidence that progesterone supplementation is beneficial in the setting of recurrent miscarriage [9]. Elsewhere, progesterone is recommended for routine use in situations such as in-vitro fertilisation [10]. Exogenous natural progesterone has no global safety issues when used in the first trimester of pregnancy [11]. Several decades of clinical use and non-clinical evidence have confirmed its safety profile, with no effect on embryo-foetal viability or malformations being identified [12].

The standard combination regimen for early medical abortion is mifepristone 200 mg administered orally, followed by 800 mg buccal misoprostol 36–48 h later [13].

Mifepristone is a synthetic steroid with high affinity for the progesterone receptor. Progesterone is essential in the maintenance and development of a pregnancy. The competitive inhibition of progesterone's endometrial and myometrial effects by exogenous mifepristone causes deterioration of the endometrium, placental disruption and demise of the embryo. Other effects in pregnancy include increasing uterine contractility and sensitivity to prostaglandins and softening and dilation of the cervix [14]. Of particular significance in the circumstance of ongoing pregnancy after mifepristone administration, evidence demonstrates that mifepristone has no teratogenic effect on the embryo [15], a position which is also held by the American Congress of Obstetricians and Gynecologists [16].

The time-delay between administration of mifepristone and subsequent completion of the medical abortion protocol by taking misoprostol is 24–48h. This period may give women time to think more about their decision and, for some, to change their minds. In such circumstances, a number of women have reported that recommendations from abortion-providers have been to continue with the medical abortion protocol and that women had 'no choice' but to do so [17]. Women in Australia faced with this have sought treatment with progesterone in order to try and save their pregnancy [18] and are the subject of the present report.

Materials and methods

Once a woman made contact with a clinically staffed national pregnancy support service, usually via internet search, she was advised that she had three options: (1) do nothing at all and see if her pregnancy continues or miscarries; (2) continue with the medical abortion process and take the misoprostol; and (3) seek consultation with a doctor willing to prescribe progesterone. Women requesting progesterone were fully informed and given written information. Those wishing to proceed with progesterone treatment provided informed consent for this, including for collection of demographic and treatment/outcome data. If she was <48h since taking mifepristone and she had not taken misoprostol, then she was commenced on progesterone vaginally: 400 mg twice a day for 3 days, then 400 mg at night for the next 6 days, then 200 mg at night for the next 6 days. A pelvic ultrasound scan was arranged to assess pregnancy viability and a follow-up appointment was made for 72h after commencing progesterone treatment. After two weeks of progesterone, the pregnancy was managed with routine antenatal care on the assumption that the projected duration of action of mifepristone had been overcome [19].

De-identified clinical and demographic data for the present study was provided by the pregnancy support service for secondary analysis by a clinician not involved in care of the women. This project received approval by the Human Research Ethics Committee of the University of New England (HE17-198).

Results – case series

Patient N

A 28-year-old woman, gravida (G) 1, para (P) 0, had her last menstrual period (LMP) 43 days prior to attending an

abortion clinic. Mifepristone was ingested at the clinic and that evening she began an Internet search for how to reverse its effects. She made contact with a doctor locally and commenced progesterone pessaries within 28h of taking mifepristone. She experienced minor vaginal bleeding over the next 2 days. Pelvic ultrasound within 3 days demonstrated a gestational sac but no foetal pole; however, β -hCG level of 8708 IU/L on the day after mifepristone administration was acceptable for a gestation consistent with her menstrual dates. She completed 14 days of vaginal progesterone and follow-up ultrasound at that point showed a viable 8 week and 4 day-sized gestation. The remainder of the pregnancy was uncomplicated and a healthy male baby with no birth defects was delivered at 39 weeks gestation.

Patient T

A 35-year-old woman, G3 P2, had her LMP 61 days prior to attending an abortion clinic. Mifepristone was ingested at the clinic and within 90 minutes she sought to have its effects reversed. She made contact with a local doctor and commenced vaginal progesterone within 3.5h of taking mifepristone. She experienced vaginal bleeding and a pelvic ultrasound scan in the Emergency Department of a hospital demonstrated a fetal heart beat and viable pregnancy. Follow-up ultrasound a week later again demonstrated a viable pregnancy. She completed 14 days of vaginal progesterone but was then lost to follow-up until she notified the doctor of the uneventful birth of a healthy baby boy with no birth defects 7 months later, likely at term according to her menstrual dates.

Patient O

A 27-year-old woman, G2 P1, had an unknown LMP but stated she had had an ultrasound scan by an abortion provider showing a pregnancy at 7½-week gestation. She had attended an abortion clinic and ingested mifepristone on site. Within 30 min, she began searching for how to reverse its effects. She made contact with a local doctor and commenced vaginal progesterone within 31h of taking mifepristone. That night she experienced heavy vaginal bleeding with clots and, believing she had miscarried, she did not continue progesterone. Follow-up ultrasound one week after ingesting mifepristone demonstrated an empty uterus and completed abortion.

Discussion

Findings and interpretation

The cases presented here demonstrate that some women who commence the medical abortion process then change their mind and instead wish to keep their pregnancy viable. These women independently and actively sought clinical treatment in the form of progesterone in an attempt to counter or 'reverse' the effects of mifepristone.

It has been proposed that abortion is fundamental to women's health [2]. In this regard, a reversal strategy for women who change their mind presents a dependent but similarly fundamental 'reproductive choice' option. It is one, however, that has more urgent need for action given the

pharmacological/physiological actions of mifepristone, with the highest risk being in the first 1–2 days [19].

Progesterone administration to antagonise the effect of mifepristone in medical abortion is off-label since this is not an indication listed in the drug product information (PI). Drugs are commonly used off-label based on common pharmacology and existing use for comparable approved indications, or where supported by high-quality clinical evidence [20], for example present/recent use of both mifepristone and misoprostol for medical abortion [4]. Where there is lack of good evidence for efficacy but where safety has been considered, exceptional circumstances may apply whereby off-label drug use can be considered appropriate. In justifying progesterone use to reverse a medical abortion: there is a serious underlying condition; there is some evidence to support potential beneficial effect; potential benefits outweigh potential risks; and no other treatment is available or appropriate [21]. Although critics have described such progesterone treatment as ‘an affront... to the ethical practice of medicine’ [19], these criteria as well as the significant distress of women seeking this treatment appropriately justify its use. Certainly, the unwanted procured termination of an early pregnancy has fittingly been described as entailing ‘catastrophic sequelae’ [22].

Results of other studies

An early animal study compared three groups of pregnant rats: one group was administered mifepristone only, one group was coadministered mifepristone plus progesterone, and a control group was administered the drug vehicle only. Serial sacrificial measurements were taken at days 1–4 post-administration of the vehicle/agent(s). Analysis demonstrated that after 48 h from administration of the agent, the mifepristone-only group experienced a 66.7% abortion rate while the mifepristone plus progesterone group had a 0% abortion rate compared with controls [23].

One human study reported six cases in the USA where women who had taken the mifepristone component had then changed their mind and sought to counter the abortifacient effect of mifepristone on their pregnancy [24]. Their published protocol recommended progesterone 200 mg intramuscularly be administered: as soon as possible after ingestion of mifepristone, then daily for two more days, then second-daily until 13 days after ingestion of mifepristone, then twice-weekly until the end of the first trimester. In contrast, the regimen for the women discussed in the present study relied on progesterone 200 mg pessaries delivered vaginally, twice-daily for two weeks. Direct comparison of the effectiveness of either of these regimens is not possible due to the small numbers of women included. Similarly, conclusions about the actual effectiveness of progesterone treatment in countering the abortifacient effect of mifepristone, at all or for either methodology, could not be drawn – nor was that the intent of this research.

A group in the USA currently coordinates progesterone-based mifepristone ‘reversal’ internationally, with a claimed success rate (continuation of pregnancy and delivery of a baby) of approximately 55% [17]. Critics in a recent review have stated that pregnancy continuation rate after ingestion of mifepristone alone is as high as 46% [19]. This figure, however, represents the results from one clinical trial

in another published study [25] in which the original authors reported an overall continuation rate of 36.5% across all the clinical trials included. Of note is that the review included studies with faulty criteria for determining embryo survival, such as those that did not differentiate between incomplete evacuation of the uterus and embryo survival among the abortion failures. Furthermore, the review also omitted a number of other key eligible studies from their analysis [26]. The more current and correct pregnancy continuation rate for mifepristone 200 mg administered alone at ≤ 49 days gestation is $< 25\%$ [26].

Strengths and weaknesses

A significant advantage of the regimen presented here is the availability and stability of progesterone as a vaginal pessary compared with parenteral formulations. The latter presents certain barriers including requiring sterile extemporaneous compounding in Australia, reduced stability and shelf-life, higher costs and less acceptable route of administration. In contrast, progesterone pessaries can be stored for longer and be available for use at immediate notice, thus decreasing the potentially adverse lag time between ingesting mifepristone and commencing progesterone treatment. Availability of a parenteral formulation may be less of an issue in other parts of the world where such a product is industrially produced and accessible.

A weakness of this study is the small number of women whose cases were reported. As a case series, data for analysis was only available for several representative women who undertook treatment to reverse the medical abortion they had already commenced. These may represent only a fraction of women who have similarly considered changing their mind after ingesting mifepristone but who have not had the awareness or opportunity to seek progesterone treatment to try and maintain pregnancy viability.

Future questions

There is currently no definitive evidence for the success of using progesterone to prevent the abortifacient effect of mifepristone. The number of cases in the literature does not lend itself to statistical analysis but instead illustrates a low-risk intervention with the potential for substantial benefit for the individual women involved. A placebo-controlled randomised or case-control study may not be ethically acceptable; however, historical control data for abortion completion rates with mifepristone alone has been detailed [26]. Prospective research to appropriate scientific standards is recommended in order to draw substantive clinical conclusions, including investigating effectiveness, formulation and timing issues.

A recent review cited, based on a personal communication with the drug manufacturer, that of the women taking mifepristone in the USA, less than 0.004% later chose to continue their pregnancy [19]. This would indicate that 6 of the approximately 145,434 women undertaking early medical abortion in the USA in 2012 [27] had changed their mind. Elsewhere, it is claimed that since the first case in 2006, there have been over 500 women who changed their mind and sought out progesterone treatment to save their threatened pregnancy [28].

The real prevalence of women who commence medical abortion but who then seek to preserve their pregnancy is

itself a research question. A deeper field of enquiry, however, is that of the reasons and circumstances surrounding women's decisions to abort their medical abortion procedure, given the often significant psychosocial stress involved in such situations and the decision-making process.

Conclusions

There is evidence in Australia that women have changed their minds shortly after commencing early medical abortion. The use of progesterone to counter the effects of mifepristone in such cases may be clinically beneficial in preserving her threatened pregnancy. Where the possible benefit is so great, the low risk of harm from using progesterone as well as the lack of teratogenicity of mifepristone supports this indication. As well as being potentially therapeutic for her pregnancy, such emergency treatment may also address a woman's short- and long-term emotional/psychological distress, and provide her with her rightful reproductive choice options.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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