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Opinion

Have we overlooked the role of mifepristone for the medical management of tubal ectopic pregnancy?

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ABSTRACT

Ectopic pregnancy is a risk of both spontaneous and assisted reproduction pregnancies. The majority of ectopic pregnancies abnormally implant within a fallopian tube (extrauterine pregnancies). In haemodynamically stable women, medical or expectant treatment can be offered. Currently accepted medical treatment is using a drug called methotrexate. However, methotrexate has potential adverse effects, and a significant proportion of women will still require emergency surgery (up to 30%) to remove the ectopic pregnancy. Mifepristone (RU-486) has anti-progesterone effects and has a role in managing intrauterine pregnancy loss and termination of pregnancy. On reviewing the literature and given progesterone's pivotal role in sustaining pregnancy, we propose that we may have overlooked the role of mifepristone in the medical management of tubal ectopic pregnancy in haemodynamically stable women.

Keywords: mifepristone / ectopic pregnancy / methotrexate / fallopian tube / RU148

Introduction

An ectopic pregnancy abnormally implants outside the endometrial cavity of the uterus, mostly (~97% of cases) within a fallopian tube (Jurkovic and Wilkinson, 2011; Elson*et al.*, 2016). Affecting ~1% of all pregnancies (O'Herlihy, 2011; Elson*et al.*, 2016), ectopic pregnancy remains the leading cause of maternal mortality in the first trimester of pregnancy accounting for almost 3% of all pregnancy related deaths annually in the UK (Bamber *et al.*, 2022). With advances in ultrasound and biochemical markers, many ectopic pregnancies are diagnosed or suspected much earlier and, importantly, before rupture of the ectopic pregnancy when surgery is essential to stop life-threatening bleeding. Studies have found that in carefully selected cases (at lower and reducing hCG levels and if haemodynamically stable, with early stage ectopic pregnancy on ultrasound) some women can be treated medically or expectantly. Thereby providing an alternative non-surgical management compared to the traditional surgical intervention which will usually involve salpingectomy to remove the affected tube (Hajenius *et al.*, 2007; van Mello *et al*, 2013; Elson *et al.*, 2016; National Institute of Clinical Excellence (NICE), 2021). The most commonly used drug for medical treatment for ectopic pregnancy is methotrexate which has an antifolate mechanism of action and thus is harmful to active pregnancy tissue (Hajenius *et al.*, 2007; Elson *et al.*, 2016).

However, methotrexate treatment retains up to a 30% risk of requiring emergency surgery (Skubisz *et al.*, 2013; Avcioğlu *et al.*, 2014; Horne *et al.*, 2023), either due to treatment failure or in the event that rupture occurs, the latter inducing the risk of life-threatening intra-abdominal haemorrhage leading to emergency surgery to remove the affected tube despite initial medical management. Reported success rates for methotrexate treatment do vary in the literature from 65% to 90% (Kirk *et al.*, 2006; Hajenius *et al.*, 2007; Lipscomb *et al.*, 2009); however, the addition to the literature of the recently published trial of methotrexate + gefitinib versus methotrexate alone GEM3 trial (Horne *et al.*, 2023) results means we can be confident that the risk of requiring surgery despite methotrexate treatment is as high as 29% (Horne *et al.*, 2023). Furthermore, with an anti-folate effect, methotrexate is teratogenic thus in UK guidance there is advice to avoid new conception for at least 3 months after a single dose of methotrexate (Elson *et al.*, 2016; Royal College of Obstetricians and Gynaecologists (RCOG), 2016) and in many hospitals advice is given to avoid new pregnancies for up to 6 months if a second dose of methotrexate is required. Literature varies, but between 3% and 27% of women treated with methotrexate are believed to require a second dose for the treatment of ectopic pregnancy (Kirk, *et al.*, 2006). This can understandably be unacceptable for some women who may wish to try for further pregnancy as soon as possible, though evidence of the need to avoid conception due to the risks of teratogenicity after methotrexate treatment for

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ectopic pregnancy is very limited (Svirsky et al., 2009; Elson et al., 2016; Lagarce et al., 2016). In addition, treatment with methotrexate or expectant management can take many weeks for the pregnancy to resolve, leading to a prolonged period of hospital follow up, uncertainty of treatment success and pregnancy avoidance for women. Methotrexate has potential rare adverse effects including risks of liver cirrhosis, renal failure, pneumonitis, gastric ulcers, and bone marrow suppression though all are uncommon; with more common side effects including stomatitis, flatulence, and transient abnormalities in liver function tests (Elson et al., 2016). Many other medical treatments have been tried but no obvious effective alternative to methotrexate has be identified (Hajenius et al., 2007; May et al., 2018; Horne et al., 2023).

Potential role of mifepristone

Mifepristone has an anti-progesterone effect, and thus is detrimental to the progesterone needs of an early developing pregnancy. Mifepristone is widely used to induce miscarriage with a recent trial reporting the addition of mifepristone to misoprostol as superior to misoprostol alone (Chu et al., 2020), though a prior Cochrane review published in 2019 found the evidence was varied and low quality (Lemmers et al., 2019). Using mifepristone has been shown to increase effectiveness of intrauterine evacuation when used with misoprostol compared to misoprostol alone for first (Zhang et al., 2022) and second (Wildschut et al., 2011) trimester induced abortion.

The role of mifepristone in the medical management of tubal ectopic pregnancy may have been overlooked. There are two small European randomized controlled trials (RCTs) (Gazvani et al., 1998; Rozenberg et al., 2003) from around 20 years ago that addressed mifepristone as an adjuvant treatment alongside methotrexate to treat ectopic pregnancy. Gazvani et al. (1998) reports in 2 groups of 25 women an improvement from 72% to 88% with Mifepristone (odds ratio (OR) 2.85 (95% CI 0.54 to 19.17)), while Rozenberg et al. (2003) reports in 113 versus 97 women an increase from 74.2% to 79.6% (relative risk (RR) 1.07 (95% CI 0.92 to 1.25)). A further cohort study (Perdu et al., 1998) suggests that those treated with mifepristone had more successful treatment with methotrexate compared to methotrexate alone. Wan et al. (2016) published a systematic review of 36 studies from China and suggested that methotrexate and mifepristone as a combined treatment was more effective than methotrexate alone in the initial treatment of ectopic pregnancy (OR 3.66 (95% CI 2.56–5.23)), though studies published in the review article (Wan et al., 2016) appear to be of low quality. In addition, there are growing reports of mifepristone being used successfully to treat non-tubal ectopic pregnancies such as interstitial and caesarean scar ectopic pregnancy (Cillard et al., 2022). Importantly, in Rozenberg et al. (2003), the treatment effect with the addition of mifepristone was significantly greater in women with a serum progesterone $\geq$10 nmol/l (83% versus 39%; RR 2.16 (95% CI 1.06 to 4.44)) while in women with low progesterone there was no effect.

Potential biological rationale

It is believed that the Fallopian tube arises from the same embryological origin as the endometrium of the uterus and is a continuum of the endometrium including the presence of steroid hormone receptors such as progesterone receptors (Lambalk, 2020; Maclean et al., 2020). We hypothesize that mifepristone could act as an abortifacient drug in the Fallopian tube in the same way that it acts for intrauterine pregnancies, by competitively antagonizing the effect of progesterone by binding to progesterone receptors (Sarkar, 2002; Heikinheimo et al., 2003). Progesterone is essential in controlling trophoblast invasion and maintenance of a pregnancy (Halasz and Szekeres-Bartho, 2013; Duncan, 2021)—therefore we hypothesize that a pregnancy we do not want to maintain because of its location, could be treated with the antiprogesterone effects of mifepristone. Rozenberg et al. (2003) postulate similarly, though we note that their trial ended early due to no difference between study groups, some twenty years ago. As detailed above, their results show an effect in women with higher baseline serum progesterone which suggests there is a need to re-investigate the role of antiprogesterone treatment. Rozenberg et al. (2003) highlight in their discussion that higher baseline progesterone levels may indicate an ectopic pregnancy which is actively growing. However, serum progesterone was not measured in all trial participants. Given that we already know that methotrexate is less likely to work at higher hCG levels and as progesterone levels often are raised in line with a raised hCG level (Ransom et al., 1994), it is possible that mifepristone could have an adjuvant role to improve the efficacy of methotrexate including specifically in women where currently methotrexate has a higher failure rate. In addition, mifepristone could have a role in the degradation of the corpus luteum (Somell et al., 1990; Telleria et al., 2001). Again this may be particularly relevant where the corpus luteum is still active in an ectopic pregnancy driving steroid hormone production (including progesterone) and maintaining the ectopic pregnancy. Thus, we hypothesize that mifepristone could reduce the production of progesterone via the corpus luteum in ectopic pregnancy.

Conclusion and recommendations

Mifepristone is an abortifacient medication, widely available in early pregnancy units, with a low side effect profile and minimal costs. We propose that mifepristone could have a role in treating tubal ectopic pregnancy medically, either alongside methotrexate or potentially as a standalone treatment of unruptured tubal ectopic pregnancy. We hypothesize that mifepristone may be particularly effective in women with high progesterone levels at greater risk of failed treatment with methotrexate.

Existing studies indicate that mifepristone may have a positive impact on the treatment of tubal ectopic pregnancy when used in conjunction with methotrexate (Gazvani et al., 1998; Rozenberg et al., 2003). However, results of these studies must be interpreted carefully as the study designs are of low quality and small sample size. Definitive, large multicentre RCTs are needed to address this important research question. In such studies, mifepristone could be trialled as an additional treatment alongside methotrexate or as a standalone treatment for tubal and non-tubal ectopic pregnancies. We note, however, the use of mifepristone for ectopic pregnancy is not recommended by the United States of America FDA (U.S.A Food and Drug Administration (FDA), 2023) nor licenced for the treatment of ectopic pregnancy in the UK (British National Formulary (BNF), 2023), and we wish to highlight it is our opinion that there is insufficient evidence to implement mifepristone for treatment of tubal ectopic pregnancies at present, however a high quality research trial is needed. Given the recent negative trial findings of a different adjuvant medical treatment for ectopic pregnancy (Horne et al., 2023), there is an unmet need to improve the efficacy of current non-surgical management of tubal ectopic pregnancy and we propose mifepristone requires reconsideration.

Authors' roles

J.O., A.M.F.W., and B.W.M. conceived the idea for the paper. J.O., A.M.F.W., and S.B. conducted literature reviews, data extraction. Data interpretation from existing literature was conducted J.O., S.B., B.W.M., and A.M.F.W. J.O. wrote the first draft of the paper. A.M.F.W. revised the paper following journal review. J.O., S.B., A.M.F.W., and B.W.M. all contributed to each draft of the paper including the final revised version.

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Conflict of interest

B.W.M. reports consultancy for Merck KGaA and Organon and travel support and research grants from Merck KGaA. A.M.F.W. has a travel scholarship awarded from the RCOG; a research grant funded by the Tommy's UK Charity and PPI grants from the University of Aberdeen Wellcome ISSF fund including a PPI project grant to explore public and patient views on the subject of this opinion paper; and a research networking grant from the University of Aberdeen. J.O. and S.B. have no disclosure of interests.

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