

**Improving Current
Therapies and
Exploring New
Options in
Abortifacient
Technology**

Gynuity
HEALTH PROJECTS



*Improving Current Therapies and Exploring New Options
in Abortifacient Technology*

MEETING SUMMARY
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Summary:

On June 22, 2004 Gynuity Health Projects convened a small group of international experts in the field of medical abortion and women's health for a symposium entitled "Improving Current Therapies and Exploring New Options in Abortifacient Technology." In this one-day meeting held in Edinburgh, Scotland, the group discussed current activities around novel abortifacient development and debated how best to balance resources between this research and efforts to improve existing medical abortion regimens. Participants included basic science researchers, social scientists, clinicians, and pharmaceutical industry experts. Much of the meeting focused on promising research avenues and drug candidates including antiprogestins, other antihormones, prostaglandins and analogues, antifolates and antimetabolites, and angiogenesis inhibitor drugs. More broadly, participants explored the qualities of an "ideal" abortifacient, as well as the social and political considerations involved in developing and promoting new therapies. Among the priority areas identified for future collaborative work were: 1) continuing to introduce medical abortion in countries where it is currently unavailable; 2) developing single-dose regimens for mifepristone-misoprostol medical abortion; 3) establishing the minimum technology required for medical abortion; and 4) improving medical abortion for gestations >9 weeks.

ENVISIONING AN IDEAL ABORTIFACIENT: WHAT ARE WE LOOKING FOR?

Before discussing promising avenues of research on new abortifacients, meeting participants explored together the different properties that an “ideal” abortion method might possess. The group suggested the following characteristics:

1) High Efficacy. While there will never be an ongoing pregnancy rate of 0%, a rate of < 1% could be considered ideal. This was felt to be important in order to minimize the potential for teratogenic effects associated with large doses of prostaglandins during pregnancy. Furthermore, a high ongoing pregnancy rate would have important implications for health services, given the need for careful follow-up of women who had been treated. In the U.S., where many clinics have a very low ongoing pregnancy rate (reportedly around 0.5%), service delivery is actually designed as though there were a 2-4% ongoing rate. This inevitably requires greater resources and could pose practical problems in low-resource settings.

2) Single dose regimen. Administering mifepristone and misoprostol together could be more appealing to women as this would simplify the treatment protocol and avoid the need for an additional visit to receive the prostaglandin. This may also result in overall cost savings for the method. A study conducted several years ago used a slow release prostaglandin vaginal pessary of gemeprost for medical abortion in the first trimester (Cameron IT, Baird DT. *Contraception* 1986; 33:121-125). The hygroscopic pessary consisted of PGE1 (3mg gemeprost) incorporated into a strip of polyethelene oxide-based hydrogel, 30 mm in length. In this study, 12 out of 13 women treated had a complete abortion. The median quantity of prostaglandin used from the pessary was 53%. From a technological point of view, participants noted that a PGE2 (dinoprost) removable pessary is currently in existence for cervical ripening for induction of labor in pregnant women at term.

These studies raise the possibility of developing a combination of oral mifepristone and a vaginal slow-release preparation of misoprostol for a “single point in time administration” medical abortion regimen. A discussion followed on the idea of inventing an enteric-coated, time-release oral misoprostol preparation, for use with mifepristone in a single dose regimen. Although this would have potential advantages in that it would be administered orally and could have fewer GI side effects, participants felt that it might be difficult to maintain oral PG within the GI tract long enough for mifepristone to exert a significant effect.

Researchers in the U.S. are also experimenting with shorter intervals between mifepristone and misoprostol administration. The group noted research by Creinin et al, comparing mifepristone 200mg followed by vaginal misoprostol 800µg either 6-8 hours or 24 hours later, for medical abortion in women up to 63 days gestation. Findings show good efficacy for the two regimens.

3) Very low morbidity. An ideal abortifacient would have an adverse event rate of virtually 0.

4) Reduced pain. Participants suggested that an agent that caused cervical dilation prior to the onset of significant uterine activity could result in less pain, since the products of conception (POC) could be expelled through a dilated cervix with reduced uterine contractility. It was suggested that a nitric oxide donor (NO) could be a possible cervical ripening agent; indeed, NO donors have been found in some studies to be possible alternatives to induce cervical ripening in second trimester abortion.

5) Less post-abortion bleeding. An agent that caused dissolution of the placenta or re-absorption of the pregnancy might result in less bleeding and pain. Absence of bleeding altogether could also be disadvantageous as the woman might worry that she was still pregnant. It was suggested that a luteolytic agent would result in regression of the corpus luteum and lead to earlier resumption of ovarian activity with reduced post-abortion bleeding than with current medical methods.

6) Effective longer than up to 49 days gestation. Ideally, a regimen would be applicable to over 49 days LMP and would not require accurate (ultrasound) gestational age dating.

7) Effective in early but not advanced pregnancy. Participants discussed the possibility that a therapy could be used after the first missed menses in the absence of pregnancy testing, without disrupting or harming a pregnancy if taken in late pregnancy. The group suggested that such a method might be marketed as a “menstrual inducer” or “regulator.” Furthermore, such a preparation might lend itself to over-the-counter (OTC) availability.

8) Orally active. Although the preferred route of administration is partly culturally dependent, an oral preparation would likely be preferred by many women as well as be advantageous in countries where abortion is conducted under clandestine circumstances; in politically restrictive environments, vaginally placed tablets have the potential disadvantage of being “discoverable.” Furthermore, participants suggested that there could be positive psychological significance for the woman in swallowing a pill (e.g. more control, less invasive), rather than having it administered to her by a health professional.

9) Self-administered. Similarly, the ability to administer the treatment oneself may be seen as an advantage by many women and certainly simplifies service delivery.

10) Predictable and rapid return to ovulation. Since hCG levels after an abortion help to maintain the corpus luteum, a luteolytic agent that would cause regression of the corpus luteum would lead to earlier resumption of the normal menstrual cycle.

11) Provides ongoing contraception after the abortion procedure. Perhaps this could be provided by an antiprogestin-impregnated intrauterine device or vaginal ring.

12) Cost. An ideal abortifacient would be inexpensive and accessible in all countries.

NOVEL ABORTIFACIENTS: PROMISING AVENUES OF RESEARCH AND DRUG CANDIDATES

Antiprogestins: Participants viewed mifepristone as possessing many qualities of an “ideal” antiprogestin, since it is administered as a single dose (200mg), lasts 72 hours and is virtually free of side effects. Furthermore, it is relatively inexpensive to manufacture. In view of these qualities and the abundant clinical experience with mifepristone, the group felt that it would not be worthwhile investing efforts and resources in developing other antiprogestins for abortion. Similarly, participants did not believe that further studies to examine efficacy of reduced doses of mifepristone (< 200mg) were indicated, since large numbers of subjects and very low drug doses would be required to show any important difference.

Participants also discussed the simplified, reduced-dose regimen of mifepristone medical abortion, which consists of 200mg mifepristone followed by 400µg misoprostol taken at home.

Results from a recent multi-center U.S. trial testing this simplified regimen for medical abortion up to 49 days LMP show similar efficacy rates as the U.S. registration trial.

Other antihormones: A combination of a progesterone synthesis inhibitor (3 β hydroxysteroid dehydrogenase inhibitor), such as epostane or trilostane, together with mifepristone, might result in increased release of endogenous prostaglandins and have a synergistic effect on myometrial contractility. Although epostane is very difficult to obtain, trilostane is available (at least in the UK). It could be worthwhile to conduct a small study comparing uterine activity in women treated with trilostane and mifepristone and those treated with mifepristone alone, to test the hypothesis that combined treatment has therapeutic advantages. However, as detailed above, the trial would have to be quite large.

The group discussed briefly the potential of LH receptor antagonists for use as abortifacients in early pregnancy. Although such agents do not currently exist, it is likely that they will be developed in the future. Participants also discussed studies conducted with other anti-hormones such as tamoxifen and danazol, neither of which appears to be promising. Similarly, there do not seem to be any promising drug candidates at present among hCG antagonists.

Prostaglandins and analogues: Participants noted that prostaglandins alone have been proven to be effective abortifacients. Although the dose and regimens for gemeprost-only regimens have previously been established, the lowest and most effective dose regimens for misoprostol remain undetermined.

Antifolates and antimetabolites: These drugs, including methotrexate as used with misoprostol, offered no advantage over antiprogestin and prostaglandins with regard to efficacy.

Participants concluded that mifepristone with misoprostol is clearly more effective than any misoprostol-alone regimen, or regimens using anti-folates or other antimetabolites; however, establishing a single-dose regimen remains a priority for mifepristone-misoprostol medical abortion.

Angiogenesis inhibitors: Current research by Hamish Fraser's group at the Human Reproductive Sciences Unit of the University of Edinburgh, studies the manipulation of angiogenesis in the female reproductive tract. Although there are no published data on the capacity of these compounds to interrupt pregnancy in animals, it is very probable that companies that have developed angiogenesis inhibitor drugs do indeed have this data.

Current studies in Edinburgh are being done on primates (marmosets), in which ovulation occurs within two weeks of giving birth, with a > 90% chance of becoming pregnant again. His current and planned studies are examining the effects of angiogenesis inhibitors in the female marmoset reproductive tract in 1) the post ovulatory period, 2) around the time of implantation, and 3) in the post-implantation period. Although they observed a significant reduction in progesterone secretion as a result of inhibiting angiogenesis in the corpus luteum, with antibody to vascular endothelial growth factor (VEGF) they have not observed a significant effect on pregnancy rates in the treated animals. They have not examined implantation sites within the endometrium but are planning to do so.

A VEGF inhibitor in the mid- to late luteal phase (when angiogenesis is diminishing in the corpus luteum), was also associated with a significant reduction in progesterone secretion,

suggesting an effect of treatment on vessel permeability. There may be potential for other novel angiogenic inhibitors for abortion, such as inhibitors of angiotensin. Angiotensins work in part to stabilize vasculature, and there is growing interest in their role in the female reproductive tract. Two-methoxyestradiol, a weak estrogen and naturally occurring compound, has been shown to possess antiangiogenic properties.

It was suggested that if angiogenesis inhibitors were used after a missed menses, they might be combined with a prostaglandin as a form of pregnancy termination. The third week after ovulation is the time of most intense endometrial angiogenesis. The embryo itself is the site of extremely rapid angiogenesis, initiated just after implantation.

More basic science on these agents is required before they can be considered for abortifacient research. A rough timeline for developing this line of research would be ten years.

Finally, a growing body of research has provided preliminary evidence on the role of angiogenesis in normal pregnancy. So far there do not appear to be teratogenic effects of VEGF antagonists on marmosets; of those who became pregnant despite VEGF inhibition, no malformations were seen in their offspring. Certain pharmaceutical companies are investing in anti-angiogenesis therapies as well as mifepristone to treat endometriosis. The group felt that it was worth continuing research on the topic and there could even be a system of “scouts” to help to keep track of research as it progresses, to identify new leads relevant to abortifacients.

INVESTIGATING EXISTING THERAPIES TO IMPROVE EFFICACY AND ACCEPTABILITY

1) Routes of administration

Participants agreed that more research is needed to determine the comparative efficacy of the vaginal, oral, buccal, and sublingual route for misoprostol administration.

2) Dose

With the existing regimen of 200mg mifepristone followed by varying doses of misoprostol, the group felt that a priority should be to establish a “one dose fits all” regimen for up to 9 weeks LMP, rather than having separate regimens for different gestational ages.

3) Gestational age limits

All participants agreed on the importance of creating a regimen that is not dependent on ultrasound to assess gestational age. In this respect, it is important to have a method that is effective up to at least 9 weeks gestation. Similarly, medical abortion protocols should ideally not need to rely on ultrasound for assessment at follow-up visits, especially since this practice leads to higher rates of unnecessary intervention. It was pointed out that in the U.S., family practitioners are increasingly providing medical abortions and often do not have access to ultrasound. However, in some settings, hCG testing can be even less feasible than ultrasound for pregnancy dating. Instead, it was suggested that a simple screening guide could be developed to assess which women should be evaluated with ultrasound.

SOCIAL AND POLITICAL CONSIDERATIONS IN DEVELOPING AND PROMOTING NEW ABORTIFACIENTS

The group identified several important challenges with respect to abortifacient use and service delivery innovation. Putting the drugs on the Essential Drugs List maintained by the WHO

remains a priority. [ed note: now accomplished 2005.] Another challenge is translating research findings into policy. As an example, there is now a great deal of evidence that home use of misoprostol is safe and preferred by women providers, yet research to this service delivery option remains.

In the midst of these political and social challenges, the group also discussed strategies for promoting abortifacient R&D and the introduction of medical abortion in new settings. There are economic grounds alone for developing and promoting safe medical methods, based on the cost of the complications of poorly performed abortions.

Furthermore, changing the indication for use of medical methods from abortion to “menstrual induction” might increase applicability of the method, in some setting where vacuum aspiration is already used in this. Another potential strategy is to relax the restrictions on medical abortion that have been applied in some jurisdictions. For example in Germany, medical abortion is permitted up to 7 weeks gestation, but a fetal heart beat must be evident on ultrasound. Since 7 weeks is just around the limit when ultrasound can detect fetal cardiac activity, this prohibitively tight restriction means that many women are unable to access a medical method.

Finally, participants suggested that clinical studies continue to be an important strategy for introducing medical methods in new settings such as in developing countries, in part since the activity involves training service providers, empowering them to share their experiences with colleagues, and helping to advance their career objectives. Small studies with mifepristone can help gain acceptance and access where it is unavailable.

RESEARCH AND DEVELOPMENT AND THE PHARMACEUTICAL INDUSTRY

All participants agreed that a major obstacle to R&D is the difficulty of securing commercial sponsorship of studies involving medical abortion. Participants agreed that a priority should be identifying a broader number of companies, to market mifepristone.

OUTLINING AN AGENDA FOR ABORTIFACIENT TECHNOLOGY RESEARCH AND DEVELOPMENT

Balancing research efforts and priorities

Participants agreed that more scientific research is required with medical abortifacients, but that public awareness of medical methods is also needed as is continued training of physicians involved in service delivery.

Priority areas for R&D

The meeting was concluded by identifying priority activities relating to research, service delivery, and enhancing collaboration:

- A main priority is introducing medical abortion in countries where it is unavailable, particularly in developing countries. Activities aimed at influencing clinical and opinion leaders within a country are key to these efforts. Setting up a clinical study of existing medical methods with an appropriate medical team(s), possibly linked to a research project exploring a specific aspect of service delivery in that country, would interest medical opinion makers. In addition, future research might include studies with nurses and midwives as vehicles for change, in promoting medical abortion in

new settings. Large-scale programs for medical abortion should introduce existing regimens that have been shown to be safe and effective.

- Other priorities identified include determining the lowest effective dose of misoprostol that could be used with mifepristone, and the development of a single-dose mifepristone/misoprostol regimen.
- Priority was also given to fine-tuning aspects of service delivery, such as identifying the minimum technology required for safe and effective medical abortion services (including minimizing reliance on ultrasound, hCG assays) and establishing criteria for satisfying safety concerns relating to home treatment (e.g. guidelines for emergency services).
- The group highlighted the importance of improving medical abortion for women with gestations > 9 weeks LMP. Efficacy rates of 90-95% have been reported for medical abortion at 14-16 weeks (mifepristone and misoprostol regimens), but 10-12 weeks remains a “grey area,” and can also pose service delivery challenges, since closer medical supervision can be required for the procedure. Furthermore, medical abortion at these later gestations may be less acceptable to women than surgical methods. Nonetheless, surgical procedures > 14 weeks require very skilled professionals who may not always be available when such procedures are needed. In such cases medical management may be a safer alternative. Medical abortion for 2nd trimester pregnancy was seen as an important area of research.

