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Alternatives to routine ultrasound for eligibility assessment prior to early termination of pregnancy with mifepristone–misoprostol

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Objective To test the feasibility and efficacy of an approach that foregoes the routine use of ultrasound for the determination of eligibility for medical termination of pregnancy.

Design Prospective trial.

Setting Ten termination of pregnancy clinics in the USA.

Population A total of 4484 women seeking termination of pregnancy with mifepristone–misoprostol.

Methods Women provided estimates of the date of their last menstrual period and underwent pelvic bimanual and ultrasound examinations. We compared estimates of gestational age using these three methods.

Main outcome measure Proportion of women of ≤9 weeks' gestation by woman or provider estimate, but >9 weeks' gestation by ultrasound.

Results The reliance on women's report of their last menstrual period together with physical examination to determine their eligibility for termination of pregnancy with mifepristone–misoprostol would result in few women (63/4008 or 1.6%) accepted for treatment outside the current limits of standard mifepristone–misoprostol regimens used for early termination of pregnancy (i.e. ≤63 days' gestation on ultrasound).

Conclusions Last menstrual period and physical examination alone, without the routine use of ultrasound, are highly effective for the determination of women's eligibility for early termination of pregnancy with mifepristone–misoprostol.

Keywords Mifepristone, misoprostol, termination of pregnancy, ultrasound.

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Introduction

Early medical abortion with mifepristone and misoprostol may expand access to services for termination of pregnancy in many settings. A much larger range of medical practitioners can offer mifepristone–misoprostol compared with surgical abortion, which requires specialised skills and facilities. Despite the potential of medical abortion to simplify termination of pregnancy services, standard protocols often require the routine use of transvaginal ultrasound for the assessment of eligibility for the procedure. These service delivery models increase both the cost of, and the involvement of medical staff in, treatment, and may limit the availability of the method to hospital and urban sites where ultrasound is available.

Ultrasound is used to determine whether a woman is at a sufficiently early gestational age such that mifepristone–misoprostol has a very high chance of success. Mifepristone–misoprostol is generally labelled for use up to 49 days (7 weeks) from the last menstrual period (LMP), but clinical research has demonstrated that mifepristone–misoprostol regimens are highly effective up to 63 days (9 weeks) from LMP,[1–4] with any falloff in effectiveness thereafter being gradual, not sudden.[5] As a result, many providers in the USA and Europe employ evidence-based protocols offering these medications up to 63 days from

LMP. Termination of pregnancy with mifepristone–misoprostol is also used in the late first trimester (10–12 weeks from LMP) with documented success rates after 9 weeks from LMP being comparable with those achieved at earlier gestations, with some modifications in the protocol.[5–10]

Previous research has indicated a high correlation between pregnancy dating determined by clinician (based on bimanual examination and history) and that determined by sonography.[11] Women who have a clear idea of the date of their LMP tend, on average, to believe that their pregnancies are slightly more advanced than they are.[12–15] Indeed, research has confirmed that most women seeking first-trimester pregnancy termination services can accurately calculate their pregnancy duration within a margin of error that would allow for the safe use of mifepristone–misoprostol.[16–18]

Ultrasound is also used to detect ectopic and molar pregnancies, rare but dangerous conditions that are not effectively treated with the standard medical abortion regimen of mifepristone and misoprostol. However, ultrasound may not be an effective screening tool for ectopic pregnancies, especially when serum human chorionic gonadotrophin levels are below 1500 mIU/ml or in patient populations in which prevalence is low.[19–21] Routine screening of symptom-free women with ultrasound is associated with a high false positive rate and may have limited medical and economic benefits.[19] Screening for ectopic pregnancies on the basis of risk factors, symptoms and bimanual examinations may be more effective.

We undertook this observational study to investigate an alternative approach to eligibility assessment for the termination of pregnancy with mifepristone–misoprostol that foregoes the routine use of ultrasound.

Methods

This multicentre study was conducted at 10 clinics within three clinic networks: Planned Parenthood of San Diego and Riverside County (six clinics); Planned Parenthood of New York City (two clinics); Family Planning Associates Medical Group of Chicago (two clinics). All women presenting at study sites seeking early termination of pregnancy with mifepristone–misoprostol were offered the chance to participate. Eligible women ingested mifepristone, 200 mg, in the clinic, verified by direct observation. Each woman then self-administered 800 μg misoprostol. The route (oral, buccal or vaginal) and timing (6–72 hours after mifepristone administration) of misoprostol varied according to the local clinic protocol.

The study was designed to explore whether an interview and physical examination provide adequate information to reliably determine which women are eligible for mifepristone–misoprostol and which should be referred for sonography or other diagnostic tests. The study also assessed whether a symptom diary and questionnaire, together with a low-sensitivity pregnancy test and pelvic examination, could identify whether a woman had undergone a successful termination of pregnancy or received further post-treatment evaluation. The findings related to the follow-up visit are described elsewhere.[23] The Allendale Investigational Review Board reviewed and approved the study.

Women consenting to study inclusion received the standard medical abortion care provided at each clinic. During the first visit, prior to transvaginal ultrasonographic examination, women in the study were asked whether they were certain of the date of the start of their LMP. If certain, women were asked to provide the date; if they did not know the exact date, women were asked to estimate either a particular date or a number of weeks ago. The clinician then performed a pelvic bimanual examination and recorded the estimate of gestational age (in weeks) based on history and clinical examination. Clinicians performing the eligibility assessment included certified nurse–midwives, nurse practitioners, physician assistants and obstetrician–gynaecologists. Most (37/39) of the clinicians were mid-level providers (i.e. certified nurse–midwives, nurse practitioners or physician assistants). Subsequent sonographic examination provided a precise gestational age for each woman's pregnancy, on which the final determination of eligibility for mifepristone–misoprostol was based. Providers also collected demographic data from the women, including age, education and whether they had undergone any previous abortion.

Clinicians screened for ectopic pregnancies using data obtained from the patient history and clinical examination. After the clinical examination and prior to viewing the ultrasound, providers completed a checklist asking whether a woman had ongoing vaginal bleeding, an adnexal mass or pain on examination; history of ectopic pregnancy, pelvic inflammatory disease, tubal surgery or sterilisation; or an intrauterine device in place at the time the woman became pregnant. The presence of any single factor was used to 'flag' possible ectopic pregnancies. The provider then indicated whether there was suspicion of an ectopic or molar pregnancy and the specific reason for the suspicion. Where possible, the final diagnosis of aberrant pregnancy was confirmed by ultrasound or by subsequent clinical and/or laboratory examinations, and documented in study files.

All women with complete data who completed the first clinic visit were included in the analysis of correlations between provider's and women's assessments of gestational age and ultrasound assessment. We excluded women who were not pregnant, according to the provider, on the basis of ultrasound examination and women with suspected

molar or ectopic pregnancy. Women for whom the provider viewed the ultrasound before performing the physical examination were also excluded from the analysis of the provider's assessments of gestational age (n = 117). The ultrasound assessment was used to determine the final gestational age.

Our outcome of interest was whether, if we relied on LMP alone or LMP plus a physical examination for pregnancy dating, women would be offered termination of pregnancy with pregnancies too advanced for use of a standard mifepristone–misoprostol regimen, i.e. pregnancies of more than 63 days from LMP on ultrasound. All statistical tests were evaluated at the 0.05 significance level and were performed using SPSS statistical software, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

From June 2005 to February 2007, 4484 women were enrolled and assessed by ultrasound at 10 study clinics (Figure 1); background data were available for analysis in 4481 of these women. Women who did not have an intrauterine pregnancy on ultrasound (n = 94) and women without accurate ultrasound data on gestational age (n = 93) or reported LMP (n = 37) were excluded from the analyses comparing women's, provider's and ultrasound estimates. The demographics of the remaining 4257 women included in the gestational age assessment analysis are presented in Table 1.

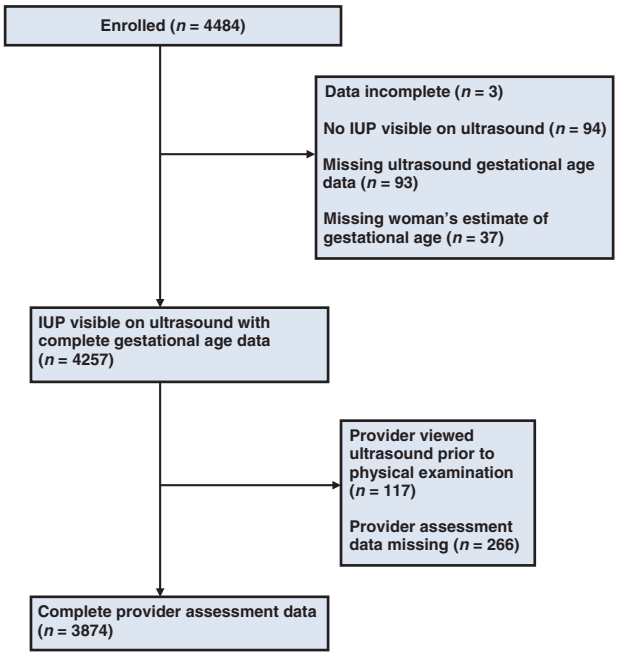

Figure 1. Flowchart of participants used in gestational age analysis.

Table 1. Patient characteristics by study site

Characteristic	Chicago (n = 1194)	New York (n = 1556)	San Diego (n = 1507)	Total (n = 4257)
Mean age (years) (±SD) (n = 4255)	27.9 (6.1)	25.0 (5.7)	25.3 (6.1)	25.9 ± 6.1
Mean education (years) ± SD (n = 4241)	14.3 ± 3.4	13.5 ± 2.3	13.5 ± 2.5	13.7 ± 2.7
Race, n (%)*				
White	770 (64.5)	183 (11.8)	1121 (74.3)	2074 (48.7)
African American	323 (27.0)	735 (47.2)	122 (8.0)	1180 (27.7)
Asian	71 (5.9)	57 (3.6)	139 (9.2)	267 (6.2)
Other/multiracial?	30 (2.5)	598 (38.4)	202 (13.4)	830 (19.4)
None of these				6 (0.1)
Ethnicity, n (%)				
Hispanic	265 (22.7)	583 (37.5)	446 (30.2)	1294 (30.8)
Non-Hispanic	903 (77.3)	970 (62.5)	1029 (69.8)	2902 (69.2)
Previous elective abortion, n (%)				
Surgical (n = 4477)	476 (39.9)	798 (51.3)	446 (29.6)	1720 (40.4)
Medical (n = 4253)	260 (21.8)	519 (33.4)	206 (13.7)	985 (23.2)
Any abortion (n = 4253)	638 (53.5)	1037 (66.6)	590 (39.2)	2265 (53.3)
Mean gestational age (days) (±SD) by ultrasound?	48.4 ± 8.2	46.4 ± 7.3	50.3 ± 9.7	48.3 ± 8.6
≤49 days, n (%)	799 (66.9)	1161 (74.6)	883 (58.6)	2843 (66.8)
50–56 days, n (%)	228 (19.1)	245 (15.7)	346 (23.0)	819 (19.2)
57–63 days, n (%)	113 (9.5)	117 (7.5)	184 (12.2)	414 (9.7)
64–70 days, n (%)	32 (2.7)	21 (1.3)	56 (3.7)	109 (2.6)
≥71 days, n (%)	22 (1.8)	11 (0.7)	38 (2.6)	72 (1.7)

*Participants could list more than one response for this question and therefore the total may exceed 100%.

Thirty-two women were flagged for suspicion of an ectopic or molar pregnancy by nonsonographic criteria (i.e. adnexal mass or pain on examination; history of ectopic pregnancy, pelvic inflammatory disease, tubal surgery or sterilisation). Nine of the 32 flagged women received a confirmed diagnosis of ectopic pregnancy and two received a confirmed diagnosis of molar pregnancy. All of these women were treated according to standard clinic protocols for these indications.

Most women (99.1%) gave a date of LMP or duration of pregnancy. Most women (70.8%) were certain of this date (data not shown). Women in San Diego were less confident in the date of their LMP, with slightly more than one-half (52.3%) reporting a 'certain' date compared with their counterparts in Chicago (79.8%) and New York (82.8%) (data not shown).

Women were very accurate in their assessment of pregnancy duration (Figure 2). Table 2 shows that, of the 3041 women with a certain LMP, only 76 (2.4%) would have been offered treatment despite being ineligible if treatment were based on report of certain LMP alone, including 13 women (0.4%) with pregnancies of ≥78 days' gestation.

As shown in Table 2, the use of certain or estimated LMP would have allowed us to evaluate many more women (4257 versus the 3041 who were certain of their LMP), whilst still resulting in inappropriate treatment in only 3.3%. Only 26 women (0.6%) would have been offered treatment at ≥78 days' gestational age.

Clinicians who had not first seen a transvaginal ultrasound (n = 4125) were able to estimate the gestational age for almost all women (3874/4125 or 96.8%) (Figure 1). If eligibility for mifepristone–misoprostol had been determined on the basis of a physical examination and history of LMP alone, only 63 of 4008 women (1.6%) would have been offered the treatment despite having pregnancies of >63 days' duration (Figure 3). Only one of these women (0.02%) had a pregnancy of ≥78 days from LMP. The determination of eligibility using clinical examination and LMP alone would have resulted in the delivery of inappropriate treatment to, essentially, almost no women.

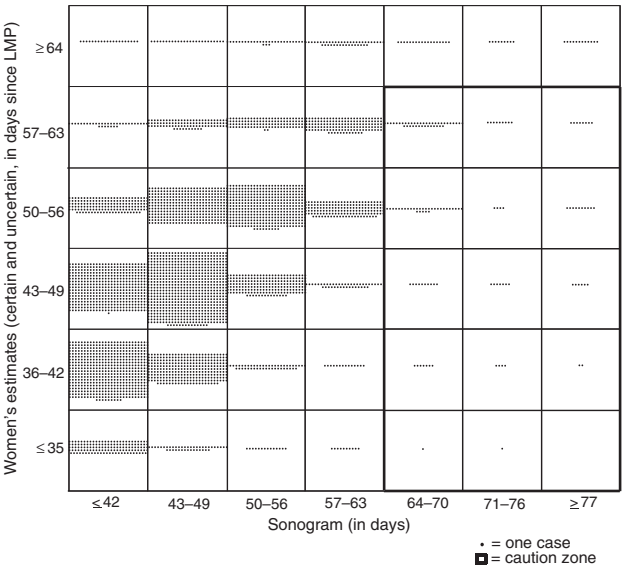

Figure 2. Women's estimates of duration of gestation compared with sonogram.

Discussion

For this study, we took the ultrasound-based estimate of gestational age to be correct, although there is also an error associated with ultrasound dating. We found that women's reports of LMP and physical examination, rather than ultrasound, to determine eligibility for medical termination of pregnancy would have resulted in few (1.6%) women receiving medical termination of pregnancy at a gestational age beyond the conventional cut-off for early medical termination of pregnancy protocols. Basing the treatment decision on certain or estimated LMP alone would have

Table 2. Gestational age by ultrasound of women who would have been incorrectly determined as eligible for medical abortion using alternative eligibility assessment techniques [n (%)]

	Gestational age by ultrasound (days)	Patient eligible by history alone		Patient eligible by physical examination and history
		Women certain of date of LMP (n = 3041 total)	Women certain or estimated LMP (n = 4257 total)	(n = 3874 total)
Gestational age too advanced according to current clinic protocols	64–70	50 (1.6)	91 (2.1)	56 (1.4)
	71–77	13 (0.4)	25 (0.6)	6 (0.15)
	≥78	13 (0.4)	26 (0.6)	1 (0.02)

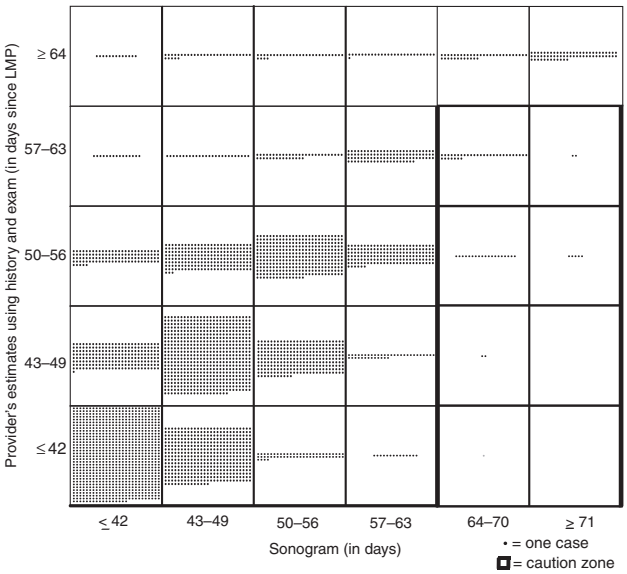

Figure 3. Provider's estimates of duration of gestation compared with sonogram.

resulted in a slightly higher (3.3%), but still very low, number of women receiving the treatment with a gestational age of more than 63 days from LMP.

Most of the women who would have been deemed eligible by LMP, but for whom ultrasound found had pregnancies that were too advanced according to current clinic protocols, presented with pregnancies in the late first trimester (64–70 days, 2.1%; 71–77 days, 0.6%; ≥78 days, 0.6%). Studies have explored the effectiveness of medical termination of pregnancy after 10 weeks from LMP, and have demonstrated the efficacy and acceptability of regimens of mifepristone and misoprostol.[5–9] Most protocols used for gestational ages above 63 days from LMP require 800 μg vaginal misoprostol in an in-clinic setting, 24–48 hours after the administration of 200 mg mifepristone, with an additional 400 μg vaginal, oral or sublingual misoprostol administered every 3 hours. As clinical research shows, the effectiveness of termination of pregnancy with mifepristone–misoprostol does not suddenly cease at 64 days of pregnancy.[5] Rather, any drop-off in efficacy is gradual, and there is evidence that the procedure remains highly effective until several weeks past the usual 63-day cut-off. When data are disaggregated, success rates for women undergoing termination of pregnancy with mifepristone–misoprostol at gestational ages of 64–70 days ranges from 92 to 98%, with no serious complications (i.e. emergency curettage, blood transfusion, hospitalisation or death). A retrospective case series of over 1000 medical terminations at 9–13 weeks found a higher rate of ongoing pregnancy among women at 78–84 days from LMP (2.1%) relative to women at 64–77 days from LMP (0.4%).[8] Rates of blood transfusion were 2.5-fold higher than the reported rates for early medical abortion, but the absolute proportion remained small (≤63 days, 0.2%; 64–91 days, 0.5%) and the relative risk was higher with later gestational ages, especially at 77 days from LMP.[8]

No studies have specifically examined the use of early mifepristone–misoprostol protocols employing the home administration of a single dose of misoprostol up to 77 days from LMP. However, evidence suggests that they still may remain safe and effective into the late first trimester, and especially at gestations of <77 days from LMP. Indeed, six women enrolled in the study with gestational ages of >63 days were administered mifepristone–misoprostol (64 days, five women; 66 days, one woman). Of these, four women had a complete abortion, and two women were lost to follow-up. One woman with a complete termination of pregnancy received empirical treatment for possible infection at the follow-up visit.

Further evidence of the effectiveness of outpatient protocols with a single misoprostol dose for gestational ages above 63 days from LMP is needed. Yet, it is already evident that, even if a few women are offered mifepristone–misoprostol at >63 days from LMP, there remains a high likelihood that the treatment will work, especially early in the late first trimester. Should it not, moreover, there would still be time to safely terminate the pregnancy in some other way.

This study constitutes a large sample of correlations between sonographic and nonsonographic diagnostic findings in women requiring medical abortion. Although standardised, some procedures may have differed across sites. We implemented a number of procedures to ensure that the clinical and ultrasound data were independent. Yet, we did not collect data on whether a woman was referred by another clinician (and thus may have received a professional assessment of pregnancy duration prior to the study visit). This appears to be a rare event but, if it were to be more frequent, it could result in an overestimation of the accuracy of both the clinical and women's assessments of gestational age. We also did not collect data on the body mass index. A physical examination may be difficult to perform in women with a large body mass index. We are unable to assess whether provider's gestational assessments were less accurate for these cases.

The current study is also not ideally suited for the evaluation of the ability of nonsonographic protocols to screen for ectopic or molar pregnancy. Although several women for whom our clinical screening questions were suggestive of ectopic or molar pregnancy did, indeed, have these conditions, our study was not adequate to fully test the reliability of such a screen. Many women who presented with signs suggestive of ectopic or molar pregnancy were directed away from the study prior to enrolment, possibly skewing our sample. A priority for future research would be to

examine systematically the relative effectiveness of clinical screens versus ultrasound for the identification of ectopic and molar pregnancies at early gestational ages. There is evidence, however, that ectopic pregnancies are less common in women seeking abortions than in the general population.[24] Moreover, women who choose to carry pregnancies to term usually do not present to clinics as early as most women seeking a pregnancy termination. The screening provided when women come for medical abortion thus allows for an earlier than usual diagnosis of ectopic and molar pregnancies in medical abortion cases than in women carrying pregnancies to term. As medical abortion also provides an ongoing contact with all women who return for follow-up, there are other occasions in the treatment process to identify ectopic and molar pregnancies should these conditions be missed at the first visit.

This study demonstrates that the reliance on women's reports of LMP together with physical examination is a highly effective method of determining eligibility for termination of pregnancy with mifepristone–misoprostol. Nearly all of the gestational age assessments were performed by advanced practice clinicians or 'mid-level providers', i.e. nurse–midwives, physician assistants or nurse practitioners. Practitioners in the USA and other high-resource countries can thus feel safe in offering these services even if their particular practices lack ultrasound equipment. These findings will also reassure providers working in low-resource settings, where ultrasound is not available and where access to safe termination of pregnancy services is severely needed.

Disclosure of interest

The authors do not have any potential conflicts of interest of a financial or other nature.

Contribution to authorship

HB participated in the design and coordination of the study and the drafting of the manuscript. WC participated in the design and coordination of the study and the drafting of the manuscript. ESL participated in the design of the study, the coordination of data collection and the review of the manuscript. SMS participated in the design of the study, the coordination of data collection and the review of the manuscript. JT participated in the design of the study, the coordination of data collection and the review of the manuscript. AB assisted with data collection and reviewed the manuscript. LA assisted with data cleaning and analysis, and the review of the manuscript. BW participated in the design and coordination of the study and the review of the manuscript.

Details of ethics approval

This study was reviewed and approved by the Allendale Investigational Review Board in May 2005 and renewed annually during enrollment. Informed consent was obtained from all women who participated in the study.

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