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Original research article

Induction of fetal demise before pregnancy termination: practices of family planning providers☆,☆☆,★

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Abstract

Objectives: Our survey aimed to characterize the practice of inducing fetal demise before pregnancy termination among abortion providers, including its technical aspects and why providers have chosen to adopt it.
Study design: We conducted a survey of Family Planning Fellowship-trained or Fellowship-affiliated Family Planning (FP) subspecialists about their practice of inducing fetal demise, including questions regarding the circumstances in which they would induce demise, techniques used and rationales for choosing whether to adopt this practice.
Results: Of the 169 FP subspecialists we surveyed, 105 (62%) responded. About half (52%) of respondents indicated that they routinely induced fetal demise before terminations in the second trimester. Providers' practices varied in the gestations at which they started inducing demise as well as the techniques used. Respondents provided legal, technical and psychological reasons for their decisions to induce demise.
Conclusion: Inducing fetal demise before second-trimester abortions is common among US FP specialists for multiple reasons. The absence of professional guidelines or robust data may contribute to the variance in the current practice patterns of inducing demise.
Implications: Our study documents the widespread practice of inducing fetal demise before second-trimester abortion and further describes wide variation in providers' methods and rationales for inducing demise. It is important for abortion providers as a professional group to come to a formal consensus on the appropriate use of these techniques and to determine whether such practices should be encouraged, tolerated or even permitted.

Keywords: Abortion; Second-trimester termination; Fetal demise; Dilation and evacuation

1. Introduction

Induced abortion is a common medical procedure for reproductive-aged women in the United States (US), with 1.06 million abortions reported in 2011 [1]. Of these, approximately 11% are performed after the first trimester [2]. These patients receive care from a smaller subset of physicians within the entire population of abortion providers; of all US abortion providers, only 64% offer procedures after 13 weeks' gestation, decreasing to 23% at 20 weeks and 11% at 24 weeks [3]. This decrease likely is due to both the greater technical skill and training needed for more advanced gestations, as well as increased political and legal hostility towards later abortions.

In recent years, debate has emerged over the practice of inducing fetal demise before terminations completed in the second trimester. Although the first case report of inducing fetal demise dates to the late 1970s [4], anecdotal reports suggest that such practices recently have become more common among abortion providers, especially since the 2003 passage of the Federal Abortion Ban and the subsequent 2007 Supreme Court decision upholding it [5–7]. The Ban, which mandates criminal penalties for any practitioner who "deliberately and intentionally vaginally delivers a living fetus," has led many providers and institutions to believe that

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inducing fetal demise before terminations could provide legal protection for abortion providers, although there has been no legal test so far [5]. Inducing fetal demise is not without controversy, as it involves risks to patients without associated medical benefit, making it difficult to justify from an ethical standpoint [6].

We sought to understand more about the practice of inducing fetal demise. Although small observational studies indicate an increase in inducing fetal demise before terminations since the Federal Abortion Ban [8], we know little about which abortion providers are inducing demise, what techniques they are using or for which patients. Furthermore, little is known about the reasons providers choose to induce demise. Our study aimed to better characterize the current state of inducing fetal demise in the US by gathering practice data from Family Planning (FP) subspecialists.

2. Material and methods

In 2010 and 2011, we anonymously surveyed both FP and Maternal Fetal Medicine (MFM) subspecialists across the country, including current fellows and faculty affiliated with the fellowships. We obtained names and emails of current and former FP fellows through the national Fellowship in Family Planning (FFP) office and also received names and emails of current affiliated FP faculty from the directors of each FFP site. With approval from the Society of Maternal Fetal Medicine (SMFM), we purchased list of names and postal addresses for SMFM members.

We invited all subjects via email to complete an online anonymous survey using KeySurvey software and subsequently sent two email reminders. We offered a $5 gift card to all participants that was not contingent upon survey completion and accessible through an anonymous link not connected to their survey answers. We asked participants to identify the region of the United States in which they practiced but not the state or institution. The study was approved by the University of California San Francisco Committee on Human Research.

The full survey included 65 questions on demographics, provision of second-trimester abortion and the practice of inducing fetal demise before abortions. "Elective" dilation and evacuation (D&E) or induction termination as a reason for abortion was not specifically defined but was distinguished from terminations for lethal or nonlethal fetal anomalies, severe maternal disease, inevitable abortion and preterm premature rupture of membranes. We asked participants to identify (a) whether their institution induced fetal demise as a step before abortion; (b) whether the individual him-/herself or others in that institution induced the fetal demise; (c) at what gestation fetal demise was routinely induced; (d) the main reason for inducing fetal demise before abortion (institutional policy, group/practice policy, physician preference or patient preference) and (e) the main method used [intraamniotic digoxin, intrafetal digoxin, intracardiac potassium chloride (KCl), umbilical cord division or other]. We asked providers to leave comments about their reasons for preferring to do abortions after inducing fetal demise.

We assessed personal abortion attitudes using a validated instrument with five questions using a five-point Likert scale. Scores ranged from 5 to 25, with higher scores representing more positive attitudes towards abortion [9]. We measured religiosity using three validated questions with true/false responses. Scores ranged from 0 to 3, with higher scores representing greater religious motivation [10].

Given a low response rate among MFM specialists, we limited our analyses here to the FP group. We report descriptive statistics using χ^2 tests, Fisher's Exact Tests, and *t* tests as appropriate, using Stata version 11.0 (Stata Corporation, College Station, TX, USA) to analyze the data.

3. Results

We identified 169 eligible respondents, including 34 current FP fellows (in 2010), 119 former FP fellows and 16 Fellowship faculty members who were not formally trained through the Fellowship but serve as Fellowship mentors, and sent online surveys to all identified providers. We received completed surveys from 105 FP specialists, for a 62% response rate. Of these, 26 were current fellows, 64 were former fellows, and 15 were Fellowship-associated faculty.

The majority of respondents were female and less than 40 years of age (Table 1). All regions of the country were represented, although respondents were less likely to work in

Table 1
Demographic characteristics of respondents (*N*=105).

Total	105 (100)
Age (years)	37 (30–69)
Female	91 (86.7)
Region	
West	32 (30.8)
Northeast	35 (33.7)
South/Southeast	10 (9.6)
Midwest	27 (26.0)
Works ≥50% of clinical time in an academic institution	93 (88.6)
Works with trainees	101 (96.2)
Abortion attitude [a]	22 (7–25)
Religiosity [b]	0 (0–3)
Number of D&Es performed per year	100 (2–2100)
Number of induction terminations performed per year	2 (0–500)
Institution allows elective induction termination	27 (25.7)
Institution allows elective D&E	88 (83.8)
Induce fetal demise before termination	55 (52.4)

Data are presented as *n* (%) or median (range).

[a] Abortion attitude was assessed using a validated instrument with five questions on a five-point Likert scale. Scores range from 5 to 25, with higher scores representing more positive attitudes towards abortion [9].

[b] Religiosity was measured using three validated questions with true/false responses. Scores range from 0 to 3, with higher scores representing greater religious motivation [10].

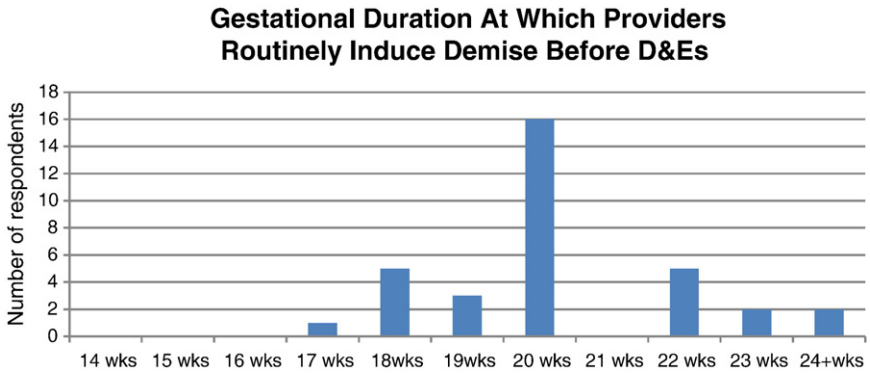

Fig. 1. Gestational duration at which providers routinely induce fetal before D&Es.

the South/Southeast region than other geographic regions. The majority of providers worked more than 50% of the time in academic institutions, and greater than 95% reported that they worked with trainees. All respondents had been trained in D&E and reported performing an average of approximately 200 such procedures annually. Only one quarter of respondents reported that their institutions allowed elective induction terminations.

About half of all respondents reported that they induced fetal demise before terminations. Seventeen respondents reported that their decision to induce demise was done on a case-by-case basis rather than a specific gestational age. However, those who based their decision on gestational duration reported thresholds spread widely throughout the second trimester, with a clustering around 20 weeks (Fig. 1). While the earliest gestation at which any provider reported routinely inducing fetal demise before D&E was 17 weeks, two respondents did not begin until 24 weeks or later. Thresholds for inducing demise before induction terminations were similarly distributed. Methods of inducing demise also varied among providers. Approximately half of respondents used digoxin, whether intrafetal (31%) or intraamniotic (22%), and a large minority reported using alternative methods, including intracardiac KCl (36%), umbilical cord transection (2%) or another method altogether (9%).

Providers who reported practicing more than 50% of the time in an academic institution, as compared to those who did not, were more likely to induce fetal demise (53% vs. 25%; p=.04) (Table 2). Providers who reported that they induced fetal demise were more likely to express more favorable attitudes towards abortion (p=.01), though both groups reported positive attitudes. Age, gender, religiosity and number of terminations performed annually were not notably different between providers who did and did not induce demise.

Reasons for inducing fetal demise included institutional policy (40%), followed by physician preference (29%), group/practice policy (21%) and finally patient preference (10%). Of the 105 respondents, 14 FP specialists chose to leave comments explaining their practice regarding fetal demise. These explanations included legal reasons, technical reasons and psychological/emotional reasons, with some respondents referencing more than one (Table 3). Providers mentioning legal reasons often expressed concern that performing an intact procedure would violate the Federal

Table 2
Institutional and individual factors associated with variation in inducing fetal demise (N=105).

	Induces fetal demise (n=55)	Does not induce fetal demise (n=50)	p value
Institutional factors			
Works ≥50% of clinical time in academic institution	52 (55.9)	41 (44.1)	.04
Works with trainees	54 (53.5)	47 (46.5)	.26
Elective terminations permitted by institution	49 (55.7)	39 (44.3)	.12
Region			
West	20 (62.5)	12 (37.5)	
Northeast	18 (51.4)	17 (48.6)	
South/Southeast	3 (30)	7 (70)	
Midwest	13 (48.2)	14 (51.9)	.32
Individual factors			
Age (years)	37 (30–69)	36 (31–65)	
Gender			
Female	49 (53.9)	42 (46.2)	
Male	6 (42.9)	8 (57.1)	.44
Abortion attitude [a]	22 (17–25)	22 (17–25)	
Religiosity (0–3 point scale)[b]	0 (0–3)	0 (0–3)	
Number of D&Es performed per year	125 (30–1000)	100 (2–2100)	
Number of induction terminations performed per year	5 (0–100)	1 (0–500)	

Data are presented as n (%) or median (range).

[a] Abortion attitude was assessed using a validated instrument with five questions on a five-point Likert scale. Scores range from 5 to 25, with higher scores representing more positive attitudes towards abortion [9].

[b] Religiosity was measured using three validated questions with true/false responses. Scores range from 0 to 3, with higher scores representing greater religious motivation [10].

Table 3
Respondents' reasons for inducing fetal demise before abortion: qualitative responses (n=14).

Legal reasons
"It may prevent legal risk of being accused of [performing a] partial birth abortion"
"Don't have to worry about legal issues"
"Do not have to worry about accidentally performing an intact procedure"
Technical reasons
"Easier to disarticulate"
"Cortical bone softening"
"Helps for advanced gestational ages"
Psychological/emotional reasons
"Personal preference"
"Easier…psychologically"
"Less drama"

Abortion Ban, whether by name or by mentioning the possibility of "breaking the law." Providers mentioning technical reasons often referred to the potential benefits of softening of fetal parts and cervical priming. Those providers citing psychological reasons mentioned concern for the emotional impact on their patients but also on the providers themselves and on the clinic and operating room staff.

4. Discussion

Inducing fetal demise before second-trimester abortion is a common practice among FP specialists in the United States, with about half of all respondents reporting that they commonly induced fetal demise.

We observed a relationship between practice environment and inducing fetal demise. Providers working in environments that are potentially more hostile to abortion were more likely to report inducing fetal demise, possibly as a self-protective measure against legal or professional repercussions. For example, we found that providers working in institutions where "elective" terminations are permitted were more likely to induce fetal demise. Popular opinion in the United States is less supportive of elective abortion procedures [11], and it is possible that providers performing such elective procedures are more likely to induce fetal demise because of increased hostility — real or perceived — in their working environments.

Many providers reported using increased gestational duration as a reason for inducing fetal demise, and we also found a trend towards increased likelihood of inducing fetal demise among providers working with trainees and/or working in academic institutions. The practice of inducing fetal demise in both situations may serve a self-protective function since later abortions have less popular support [11] and may be under greater scrutiny, especially in a clinical setting with more witnesses and observers. In addition, pressure from risk management departments of academic institutions may prompt providers to utilize this practice as a defensive legal measure. The Federal Abortion Ban and the many other recently passed laws restricting abortion provision may have contributed to providers' perceptions of a hostile and litigious environment — and to their decision to induce fetal demise as a protective measure. This interpretation is supported by comments from respondents who referred to both the concern for legal consequences, sometimes specifically referencing the Federal Abortion Ban, as well as the associated stress of potentially facing legal repercussions.

Another explanation for our findings is that providers believe that inducing fetal demise before abortion makes the procedure technically easier [12]. Several respondents mentioned improved cervical priming, fetal maceration and decreased procedural blood loss as benefits of inducing fetal demise. Although these benefits are not borne out in research [5,6,13], some providers may continue to utilize this practice based on personal experience, especially those providers who work with trainees and believe that D&E is easier to learn if the fetus is demised. Yet this explanation does not explain the finding that inducing fetal demise is more commonly done at institutions that permit elective terminations.

Individual patient factors may also influence a provider's decision to induce demise: A number of providers cited "patient preference" as their main reason for inducing fetal demise. Research on patient preferences regarding inducing fetal demise indicates that such preferences are complex, difficult to predict and substantially influenced by counseling [5,6,14–16]. Nonetheless, some individual providers may still induce fetal demise as an attempt to relieve some of their patients' perceived psychological burden associated with terminations.

We found variation in both the threshold gestational duration chosen by providers as well as the technique used. The variation in practice is understandable given the paucity of guidance available to providers, either from robust data or from professional guidelines. There is very little information available comparing methods of inducing demise to not inducing demise at all or regarding the possible patient benefits associated with these methods. Furthermore, the few studies investigating these benefits show conflicting results and mostly rely on case reports or retrospective data rather than randomized controlled trials. There have been no literature reviews or meta-analyses published examining these smaller studies. The Society of Family Planning 2010 Clinical Guideline reviewed these data and concluded that there was inadequate evidence to recommend inducing fetal demise to increase the safety of D&E, although they did not recommend against it [5]; the American College of Obstetricians and Gynecologists, in its 2013 Practice Bulletin on Second-Trimester Abortion, likewise merely reiterates the absence of supporting evidence [13]. As a result, practitioners in the field largely are left to make these clinical decisions on their own, without either definitive data or professional guidelines to direct their choice of whether to induce demise. It is notable to that almost half of all

respondents did not induce fetal demise routinely at any gestational age, further reflecting a broad variation in practice patterns. Some providers argue that, in the absence of any proven patient benefits associated with the practice, inducing fetal demise should never be routinely used before D&Es [6].

There are several possible limitations to our study. Response bias is possible; the overall response rate for our survey was 62%, and nonrespondents may have differed in their demographics and practices. One possibility is that providers who endorse more favorable abortion attitudes may have been more likely to respond to the survey. As this characteristic was associated with a greater likelihood of inducing fetal demise in our study, this could lead to an overestimation of how common the practice is among FP providers. However, while this scenario would bias our estimate of the overall percentage of providers inducing fetal demise, it should not influence our results regarding the wide spectrum of techniques and rationales for inducing fetal demise among those who responded.

Because we did not collect institutional information from respondents, we were unable to account for any clustering effect in our analyses. Further, our survey did not include non-Fellowship-trained providers who perform second-trimester abortions and included only 12 respondents who practice mainly outside of academic medicine. Accordingly, our findings may not be generalizable to this population of providers.

The strengths of our study included the wide range of respondents across geographic locations and clinical practice institutions, and the use of both categorical and open-ended survey questions to understand providers' decisions to induce fetal demise.

More research is needed to understand why the practice of inducing fetal demise has become so popular among abortion providers — whether for legal, technical or psychological justifications — as well as additional well-designed trials to assess whether these justifications are supported by data. Furthermore, given concerns over the ethical nature of some forms of inducing demise, it is important for abortion providers as a professional group to come to a formal consensus on the appropriate use of these techniques and to determine whether such practices should be encouraged, permitted or even tolerated.

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Short communication

Effectiveness and safety of digoxin to induce fetal demise prior to second-trimester abortion

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Abstract

Background: The study was conducted to assess the effectiveness in inducing fetal demise through digoxin injection given 1 day prior to second-trimester pregnancy termination and to evaluate related maternal safety.
Study Design: A retrospective cohort analysis of 1795 pregnant women between 17 and 24 weeks' gestation who received varying doses of digoxin by transabdominal intrafetal or intra-amniotic injection at the time of laminaria placement was conducted. Fetal heart activity documented by M-mode Doppler sonography on the subsequent day was considered failure. Digoxin dosages started at 1.0 mg for intrafetal and 0.5 mg for intra-amniotic injections and were progressively decreased based on best clinical judgment.
Results: The overall rate of failure to achieve fetal demise was 6.6% (95% CI, 5.5–7.9). Failure rates varied according to route of administration and dosage. There were no failures using a 1.0-mg intrafetal dose, but failures occurred with lower doses. Failure rates were higher with 0.5 mg for intra-amniotic (8.3%) than intrafetal administration (3.6%). There were no adverse maternal events at any of the doses in this study.
Conclusion: Intrafetal digoxin injection at a dose of 1.0 mg is safe and effective for fetal demise prior to pregnancy termination in the second trimester. Significantly lower doses are effective in most cases. Additional doses merit further testing.

Keywords: Digoxin; Fetal demise; Abortion; Second trimester

1. Introduction

Intra-amniotic and intrafetal digoxin are widely used regimens to induce fetal demise prior to pregnancy termination [1]. There is, however, little published information regarding the safety and effectiveness of digoxin. A single study of eight women who were intensively monitored after a 1.0-mg intra-amniotic dose of digoxin identified no adverse maternal cardiac effects [2]. In a larger study of this dose, fetal demise was not achieved in 5 of 62 subjects (8%); women who received digoxin injection were more likely to report vomiting than women who received saline injection (16% vs. 3%) [3]. The majority of women participating in that study preferred fetal death to occur prior to the abortion.

Starting in November 2003, the Parkmed Women's Center in New York City adopted a policy of using digoxin injection to induce fetal demise prior to second-trimester surgical abortions in which the fetus had a gestational age greater than 17 weeks. Due to a paucity of information regarding the minimum effective dose of digoxin, the clinic evaluated different doses, and also compared using intrafetal vs. intra-amniotic administration. This retrospective cohort analysis assesses the safety and success of different doses and routes of administration of digoxin in achieving preabortion fetal demise.

2. Methods

Data regarding the dose and route of digoxin administration, the fetal biparietal diameter (BPD), gestational age by history, patient age, and the presence or absence of cardiac

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activity the next day were routinely collected in an electronic database for quality assurance. The Columbia University Institutional Review Board gave approval to analyze these variables from an anonymized subset of the database that had all protected health information removed.

All patients who presented to Parkmed Women's Center in New York City for termination of pregnancy between 17 and 24 menstrual weeks' gestation (as measured by BPD on ultrasound) between November 2003 and February 2006, who received digoxin for fetal demise as part of standard care, and who returned to complete the dilation and extraction (D&E) procedure were included in this analysis. Patients were screened for reported allergy to digoxin, allergy to digibind, allergy to intravenous anesthesia, chronic diuretic use, chronic renal failure on dialysis, and known cardiac conduction disorder or other cardiac disease.

All patients gave informed consent for laminaria placement, digoxin injection, and D&E, after which they underwent a vaginal examination and sonography to determine gestational age. Digoxin injection and laminaria placement took place utilizing intravenous sedation with propofol and fentanyl 1 day prior to the planned D&E procedure. Laminaria insertion followed digoxin injection per clinic routine.

Patients received digoxin by transabdominal intra-amniotic injection (TAIAI) or transabdominal intrafetal injection (TAIFI) based on clinical judgment and gestational age. Patients between 17 and 19 weeks' gestation underwent either the TAIAI or TAIFI procedure. Patients with a gestational age of 20 weeks or greater usually underwent TAIFI. For TAIFI, an 18- or 20-gauge spinal needle (3.5–6 in. long) was inserted through the abdominal wall and directed under sonographic guidance to the location of the fetal heart region (or amniotic cavity) to deliver the desired dose of digoxin. Needle tip location and the delivery of the drug into the predetermined fetal region were confirmed with the appearance of an echogenic area/cloud emanating from the needle's tip. Similarly, proper intra-amniotic infusion was confirmed by the appearance of a jet flow and disturbance of the intra-amniotic debris.

Digoxin injections were carried out by only two physicians. Dosages started at 1.0 mg for TAIFI and at 0.5 mg for TAIAI and were progressively decreased to 0.125 mg when failures occurred; the dose was then increased to the previously successful level. The number of failures required to increase the dosage was based on the providers' clinical judgment. The clinical goal was to identify the minimum effective digoxin dose in order to avoid maternal toxicity.

After digoxin injection and laminaria placement, the patient was monitored in the recovery room with three-lead ECG and pulse oximetry by a registered nurse with supervision by an anesthesiologist. All patients were queried about the occurrence of palpitations and visual disturbances; the occurrence of nausea and vomiting was not entered into the study database. Vital signs were monitored every 15 min for 45 min, and patient stability was confirmed prior to discharge. On the subsequent day, all patients had repeat sonograms prior to commencing the D&E procedure. Uterine tenderness and temperature were assessed as signs of infection. Presence of fetal heart activity, as ascertained by M-mode Doppler and documented with a printed record, was considered treatment failure. For cases that delivered or had D&E at an outside facility, we used the report from the treating physician regarding the presence or absence of fetal heart activity.

Because the menstrual gestational age by history was sometimes missing or imprecise, we present all results according to the fetal BPD obtained on the day of treatment. All data analyses are descriptive, reporting the percent treatment failure with exact binomial 95% confidence intervals stratified by injection site, dose, and BPD. We used the Mantel–Haenszel extension χ^2 test to test for dose–response relationships.

3. Results

There were 1796 cases in the database. Nine women received a digoxin injection but experienced spontaneous contractions and were sent to the hospital prior to the scheduled return visit (0.5%). Seven of these had received intrafetal and two had received intra-amniotic digoxin. One of the cases with an extramural delivery was missing a BPD measurement who we thus deleted

Table 1
Failure rates for intra-amniotic digoxin injections by dosage and gestational age

Dose of digoxin (mg)	Gestational age (BPD)				Total	
	30–45 mm		46–60 mm			
	n/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)
0.125	10/21	47.6 (25.7–70.2)	0/1	0.0 (0–97.5)[a]	10/22	45.5 (24.4–67.8)
0.25	12/16	75.0 (47.6–92.7)	2/4	50.0 (6.8–93.2)	14/20	70.0 (45.7–88.1)
0.375	14/53	26.4 (15.3–40.3)	na	na	14/53	26.4 (15.3–40.3)
0.50	1/33	3.0 (0.1–15.8)	2/3	66.7 (9.4–99.2)	3/36	8.3 (1.8–22.5)
Total	37/123	30.1 (22.1–39.0)	4/8	50.0 (15.7–84.3)	41/131	31.3 (23.5–40.0)

na=not applicable, dosage not given for that gestational age.

[a] One-sided, 97.5% confidence interval.

Table 2
Failure rates for intrafetal digoxin injections by dosage and gestational age

Dose of digoxin (mg)	Gestational age (BPD)								Total	
	30–45 mm		46–50 mm		51–55 mm		56–60 mm			
	n/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)	*n*/*N*	% (95% CIs)
0.125	12/83	14.5 (7.7–23.9)	0/9	0.0 (0.0–33.6)[a]	2/4	50.0 (6.8–93.2)	0/2	0.0 (0.0–84.2)[a]	14/98	14.3 (8.0–22.8)
0.25	3/26	11.5 (2.4–30.2)	10/213	4.7 (2.3–8.5)	13/195	6.7 (3.6–11.1)	2/9	22.2 (2.8–60.0)	28/466	6.0 (4.0–8.6)
0.50	1/27	3.7 (0.1–19.0)	2/140	1.4 (0.2–5.1)	17/413	4.1 (2.4–6.5)	16/396	4.0 (2.3–6.5)	36/993	3.6 (2.6–5.0)
1.000	0/42	0.0 (0.0–8.4)[a]	0/20	0.0 (0.0–16.8)[a]	0/27	0.0 (0.0–12.8)[a]	0/18	0.0 (0.0–18.5)[a]	0/107	0.0 (0.0–3.4)[a]
Total	16/178	9.0 (5.2–14.2)	12/392	3.1 (1.6–5.3)	32/669	4.8 (3.3–6.7)	18/425	4.2 (2.5–6.6)	78/1665	4.7 (3.7–5.8)

[a] One-sided, 97.5% confidence interval.

from the database, leaving 1795 cases for analysis. No other women were excluded or missing. The mean patient age was 23.1 years (SD 6.4), and their mean weight was 152.4 lb. (SD 36.5). The fetal BPDs ranged from 30 to 60 mm.

The majority of patients received an intrafetal injection (1664/1795, 92.7%) with doses ranging from 0.125 to 1.0 mg digoxin; 7.3% of patients (131/1795) received an intra-amniotic injection with doses ranging from 0.125 to 0.50 mg digoxin. The overall failure rate was 6.6% (95% CI, 5.5–7.9). Failure rates varied according to route of administration and dosage.

For TAIAI, the overall failure rate was 31% (Table 1). The only subgroup with an acceptable failure rate, defined as less than 5%, had a BPD of 45 mm or less and received a digoxin dose of 0.5 mg; only 1 of the 33 patients in this group had a failure. There was a dose-response effect among the patients with a BPD of 30–45 ($p<.01$). Because of the higher failure rates, the use of TAIAI was shortly discontinued if the BPD was greater than 45 mm.

For TAIFI, the overall failure rate was 4.7% (Table 2). Effectiveness of TAIFI increased with digoxin dose ($p<.01$), and no failures occurred with a dose of 1.0 mg. Only 107 patients received that dose; thus, the upper 97.5% confidence interval for the failure rate is 3.4%. For patients receiving TAIFI, effectiveness did not vary according to the BPD of the fetus.

None of the patients who received TAIAI or TAIFI reported adverse events suggestive of digoxin toxicity such as palpitations or visual disturbances. We have no patient-level information available for analysis regarding nausea and vomiting; however, during this interval, clinic anesthesia practices remained constant and the use of anti-emetic medication in the clinic did not increase. This finding argues against a large increase in complaints of nausea and vomiting. Failure rates within dose/gestational age strata were similar at the beginning and end of this study which argues against an important effect of the physician learning curve.

4. Discussion

For practitioners who wish to achieve fetal demise prior to D&E, intrafetal or intra-amniotic digoxin at low doses is often effective without maternal adverse events. In this analysis, the highest dose tested was 1.0 mg digoxin, which was effective without adverse events. The safety of the 1.0-mg dose is based on only 107 patients, so further study may be warranted to identify rare, subtle or transient adverse effects that were not observed in this study. Reassuringly, 993 patients received the 0.5-mg intrafetal dose without complications. Intrafetal injection of digoxin was easily achieved with the use of maternal intravenous sedation. Whether intrafetal (especially intrathoracic) injection of digoxin would be as easily achieved without intravenous sedation cannot be addressed from these data. Intra-amniotic digoxin is easier to administer, particularly in the unsedated patient; however, it was much less effective in producing fetal demise than intrafetal injection at the doses studied here.

These results are particularly reassuring with regard to patient safety. Future studies might consider using alternate intrafetal targets and a wider range of digoxin doses to define effectiveness and safety more precisely. We also need to assess the acceptability of this treatment among unsedated patients. Where fetal demise prior to induced abortion is preferred or necessary, a single dose of intrafetal digoxin, administered 24 h prior to the procedure, is often effective.

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Review Article

Society of Family Planning clinical recommendations: Cervical preparation for dilation and evacuation at 20–24 weeks' gestation ☆,☆☆

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ABSTRACT

Although only 1.3% of abortions in the United States are between 20 and 24 weeks' gestation, these procedures are associated with elevated risks of morbidity and mortality. Adequate cervical preparation before dilation and evacuation (D&E) at 20–24 weeks' gestation reduces procedural risk. For this gestational range, at least one day of cervical preparation with osmotic dilators is recommended before D&E. The use of overnight osmotic dilators alone is sufficient for most D&Es at 20–24 weeks' gestation. Dilapan-S® dilators require a shorter time to achieve maximum dilation, may be more effective than laminaria and may increase the likelihood of success on the first D&E attempt. The use of adjunctive mifepristone administered one-day pre-operatively at the time of osmotic dilator placement, should be considered because evidence demonstrates that it makes D&E subjectively easier at 20–24 weeks without increasing side effects. While older studies suggest that two-days of serial osmotic dilators provide greater dilation than one day of dilators, adjunctive mifepristone may be comparable to a second day of dilators. Adjunctive misoprostol administered on the day of D&E does not appear to affect initial cervical dilation and procedure time and compared with mifepristone is associated with more side effects, such as pain and nausea. Using overnight mifepristone and same-day misoprostol without osmotic dilators at 20–24 weeks' gestation lengthens D&E procedure time and appears to increase immediate complications, at least among less experienced providers. Some evidence shows the feasibility of same-day cervical preparation before D&E at 20–24 weeks using Dilapan-S® with adjunctive misoprostol or serial repeat dosing of misoprostol, but same-day preparation should be limited to providers with significant experience with these regimens. The Society of Family Planning recommends preoperative cervical preparation before D&E at 20–24 weeks' gestation. Further studies are needed to clarify the best means of preparing the cervix in order to minimize abortion complications and improve outcomes in this gestational range.

Contents

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1. Introduction

In the last several years, multiple randomized trials have evaluated methods of cervical preparation before dilation and evacuation (D&E) abortion. The results of these trials have led to improvements in cervical preparation. The Society of Family Planning (SFP) is writing this update due to new evidence regarding cervical dilation before D&E at 20–24 weeks, including data on the use of the anti-progesterone mifepristone, use of osmotic dilators with and without misoprostol, and side effects of misoprostol. As a result, we are able to refine our 2008 recommendations [1]. This document synthesizes evidence from studies that used varying methodologies and patient populations. The gestational age of interest for these recommendations is 20–24 weeks, which is the range with the most consistent data reported in previous studies (20–24 weeks, inclusive). However, data from some studies using gestational ages outside the range of interest (12–26 weeks, inclusive) are included in these recommendations.

2. Background

Approximately 1.3% of abortions take place after 20 weeks' gestation in the United States each year [2]. Despite a recent decrease in the number of abortions occurring annually in the United States, the proportion of second-trimester abortions has remained relatively consistent. The vast majority of second-trimester surgical abortions are provided by D&E. Although complications from D&E are rare, the rate of such complications increases with gestational duration [3,4]. In a review of almost 12,000 patients undergoing D&E at gestations of up to 26 weeks, the most common complications included cervical laceration and blood loss of more than 500 mL, each of which occurred in less than 0.9% of patients [5].

D&E is a safe procedure, with rates of morbidity and mortality significantly lower than those associated with childbirth [5–7]. Decades of data and practice demonstrate that to minimize risk, the uterine cervix must be prepared before the procedure [8]. Three main methods are available to dilate or soften the uterine cervix before D&E: mechanical dilation with rigid dilators, preoperative placement of osmotic dilators, and preoperative administration of pharmacologic agents.

Before the advent and study of other methods, mechanical dilation was used without cervical preparation, generally with graduated rigid Pratt, Denniston, Hegar, or other mechanical dilators. Compared with use of osmotic dilators or pharmacologic agents, use of mechanical dilation alone is associated with higher risks of short- and long-term morbidity, especially because D&Es at advanced gestations require greater cervical dilatation [9,10]. In contemporary abortion practice, after 14 weeks' gestation, most providers use mechanical dilation only in conjunction with other methods of cervical preparation.

2.1. Osmotic dilators

Two types of osmotic dilators are available for cervical preparation. The dried, rolled, sterilized seaweed stems of *Laminaria japonica* expand slowly by absorbing fluid. The maximum clinical effect of this method is achieved after 24 h [11,12], with laminaria expanding to approximately 2.7–2.9 times their dry diameter [12]. Dilapan, a synthetic osmotic dilator, dilates the cervix more quickly, evenly and consistently than laminaria. Although these synthetic dilators initially were prone to fracture [13,14], they were reformulated in 2002 and replaced with Dilapan-S®. Dilapan-S® not only dilates faster than the previous formulation but has a stronger core to reduce fragmentation. Dilapan-S® dilates to almost its maximum diameter (3.3–3.6 times its dry diameter) in 4–6 h, but continues to dilate over the course of 24 h [12].

2.2. Pharmacologic and other methods

Prostaglandins and anti-progesterones are pharmacologic agents frequently used for cervical preparation. The most common prostaglandin used for cervical ripening is misoprostol, a PGE_1 analogue, which is relatively inexpensive and stable at room temperature. The World Health Organization recognizes misoprostol as one of the essential core medications necessary for basic health care [15]. Although it can be used by different routes for other purposes, to prepare the cervix before D&E misoprostol primarily is administered buccally, vaginally, or sublingually. Serum levels are lower for the buccal route, but similar uterine tone is produced with all three routes [16,17].

Mifepristone is an anti-progesterone steroid that binds avidly to progesterone receptors to cause significant cervical ripening [18,19]. Typically given orally 24–48 h before D&E, mifepristone does not have misoprostol's gastrointestinal or pyrexic side effects.

3. Clinical questions

1. *Does the use of osmotic dilators decrease the risk of D&E complications at 20–24 weeks' gestation?*

Preoperative cervical preparation reduces D&E morbidity. Mechanical dilation alone is associated with more complications than the use of osmotic dilators [9,20]. Cervical laceration with hemorrhage is one of the most commonly cited serious complications of D&E through 24 weeks' gestation [4,20,21]. Evidence from a large retrospective study that looked at complications before and after the introduction of osmotic dilators suggests that cervical preparation with osmotic dilators before D&E decreases the risk of cervical laceration [20]. This series of 11,747 D&Es completed between 1972 and 1981 evaluated the incidence of cervical laceration requiring repair at gestations of more than 19 weeks. Ten percent of all D&Es using mechanical dilation alone resulted in a cervical laceration needing repair. After the use of osmotic dilators was introduced, repaired cervical laceration decreased significantly, to 1.2% ($p < 0.05$). Early data on abortion morbidity show cervical injuries are more common among adolescent patients at any gestation [22]. However, no recent data examine this risk for adolescents undergoing an abortion after 20 weeks of gestation. Several large reviews of abortion complications have not found an association between cervical injury and parity or prior vaginal delivery [7,10,27,29].

Although uterine perforation is a rare complication, cervical preparation with osmotic dilators may decrease this risk as well. In a study describing more than 67,000 surgical abortions in which the incidence of uterine perforation was found to be 0.9 per 1000

abortions, the use of laminaria for dilation had a protective effect, although this effect was not statistically significant (RR 0.17, 95% CI, 0.02–1.20) [22]. Evidence also suggests a higher incidence of cervical injury and perforation when abortions are completed by inexperienced providers; it is unclear whether osmotic dilation modifies this risk [9,22]. No studies have examined whether use of osmotic dilators at 20–24 weeks' gestation affects the incidence of infection or hemorrhage.

2. *What are the risks of using osmotic dilators for cervical preparation before D&E at 20–24 weeks' gestation?*

Onset of labor or extramural delivery are potential rare complications after placement of osmotic dilators, with the exact incidence unknown. However, when a feticidal agent is used in conjunction with osmotic dilators, the reported incidence of expulsion or contractions leading to hospitalization ranges between 0.3% and 1.9%. Intra-amniotic digoxin causes a higher incidence of extramural delivery than intra-fetal injections [23–25].

No trials have directly examined the risk of infection after the placement of osmotic dilators for D&E at 20–24 weeks of gestation. Case reports of infection attributable to osmotic dilator placement alone are rare [14,26,27]. Antibiotic prophylaxis usually is administered at the time of dilator placement, which likely contributes to the low incidence of infection.

Currently, no data link use of osmotic dilators followed by D&E with an increased risk of preterm birth in subsequent pregnancies. A retrospective, case-control study evaluated patients who underwent D&E at 12–24 weeks' gestation and compared them with patients who did not have a prior D&E. Cases included 85 patients with a prior D&E and 170 controls. Patients with a prior D&E delivered slightly earlier (38.9 weeks vs. 39.5 weeks, $p = 0.001$). However, no statistically significant difference was found in terms of birth weight, spontaneous preterm delivery, abnormal placentation, or complications overall [28]. A retrospective review of 600 patients who underwent D&E at 14–24 weeks' gestation (average 19 weeks) after approximately 24 h of cervical preparation with laminaria identified 96 subsequent pregnancies. The researchers did not find an association of D&E with preterm birth [29]. Another retrospective cohort study described the subsequent pregnancies of patients who underwent pregnancy termination at 17–24 weeks for preterm premature rupture of membranes (without signs of labor or cervical dilatation), fetal anomalies, or fetal demise. Patients had a choice of labor induction or D&E. Those who underwent D&E after 1–2 days of osmotic dilation with laminaria had a lower incidence of preterm birth than those who underwent induction (6.9% vs. 30.2%, $p < 0.01$) [31]. The 6.9% rate of preterm birth reported in this study is substantially lower than the overall risk of preterm birth in the United States, which is 12% [30]. The authors concluded that D&E is not associated with subsequent preterm birth.

3. *What type of osmotic dilator is preferable for preparation of the cervix before D&E at 20–24 weeks' gestation?*

Both laminaria and Dilapan-S® are safe and effective osmotic dilators for cervical preparation. Dilapan-S® dilates more quickly and to a larger diameter than laminaria, requiring less time and fewer dilators for the same dilation effect and making their use an option for same-day cervical preparation in early second-trimester cases. Ultimately, osmotic dilator choice is based on individual provider preference, with little available information comparing the two. Dayananda and colleagues completed a double-blinded trial that randomized patients ($N = 180$) to overnight laminaria or overnight Dilapan-S® [31]. They stratified by gestational duration, with an early cohort at 18–20 6/7 weeks and a late cohort at 21–23 6/7 weeks. The primary outcome was operative time. Secondary outcomes included number of dilators placed, initial dilation, need for mechanical dilation, ability to complete procedure on first attempt, acceptability, and complications. Although no differences were found in operative time in either the early ($p = 0.60$) or the late ($p = 0.78$) gestational cohorts or in initial dilation and patient satisfaction, 24 D&Es were unable to be completed on the first attempt. Of those, 75% had received laminaria, suggesting a greater degree of efficacy when Dilapan-S® is used for cervical preparation instead of laminaria. In addition, Dilapan-S dilates more rapidly, which may be preferable when attempting to shorten the preoperative duration.

4. *How many osmotic dilators should be placed?*

No data address the question of how many osmotic dilators to use before D&E at 20–24 weeks' gestation, nor whether specific sizes of dilators should be used. In addition, no studies address these questions specifically for nulliparous patients or adolescents, both groups at higher risk of D&E complications [9,23,34–37]. Some experts recommend placing as many dilators as possible until resistance is met or until they fit snugly [13]. Most suggest increasing the number of dilators used as gestational duration advances because the cervix must accommodate larger forceps and the fetal parts are larger [32]. Dilapan-S® osmotic dilators achieve greater dilation than laminaria, which means fewer may be necessary at a given gestation.

One prospective investigation from 1996 that included gestations through 19 weeks observed the dilation achieved after overnight use of laminaria. The authors found that laminaria expanded more at later gestations than at earlier gestations, which they hypothesize is the result of greater cervical compliance as the pregnancy advances [33]. A review of 147 patients described the degree of dilation achieved with overnight Dilapan-S®, with or without misoprostol, before D&E at 20–24 weeks' gestation. The results suggested that two or three dilators were superior to a single dilator. Patients with a single dilator were almost 1.8 times (95% CI 1.4–2.3) as likely as those with 2–3 to require additional mechanical cervical dilation [34]. No differences in complication rates were noted between the two groups, but the study did not have adequate power to examine this outcome.

Overall, the available data are not sufficient to provide guidance about the exact number of dilators to use when preparing the cervix for late second-trimester D&E or about the effect of this number on important clinical outcomes. In a 2013 cross-sectional survey of abortion facilities in the United States, White and colleagues assessed second-trimester surgical abortion practices. Of 703 facilities across the country, 383 (54%) responded. In the second trimester, 85% of clinicians used osmotic dilators for cervical preparation. Also, 75% used misoprostol, while only 8% used mifepristone. About 75% combined dilators and misoprostol [35].

5. *Are multiple days of cervical preparation warranted before D&Es at 20–24 weeks' gestation, and if so, when?*

Previous data from a 1982 RCT [36] showed two days of laminaria produced more dilation than a single day. However, new data suggest alternatives to this practice. Recent studies have shown that overnight cervical preparation can be effective before D&Es at 20–24-weeks' gestation. A randomized controlled trial by Shaw and colleagues among patients between 19 and 23 6/7 weeks' gestation compared overnight laminaria and mifepristone to two days of serial laminaria [37]. All patients also received misoprostol on the day of their procedure. This non-inferiority trial set a 5-min difference in procedure time as being clinically significant. Mean procedure times were similar in the two groups (11 min and 52 s

among mifepristone with overnight dilators vs. 10 min and 56 s among patients receiving two days of dilators without mifepristone). The 95% CI for change in procedure time was −4:09 to +2:16 min. Patients were much more satisfied with overnight preparation with laminaria and mifepristone than with two days of osmotic dilators. This suggests two-day dilation is not necessary for routine cases. However, some cases may warrant greater dilation (for example, in certain fetal anomalies or for a more intact specimen) and some cervixes may be less responsive, requiring additional time or dilators; therefore, care must be individualized.

In a multicenter, randomized controlled trial by Goldberg and colleagues [38], subjects between 16 and 23 6/7 weeks' gestation were randomized to one of three arms: overnight dilators alone, overnight dilators with mifepristone, and overnight dilators with preoperative misoprostol. Of 300 participants, only two (one in the dilator-with-mifepristone group and one in the dilator-with-misoprostol group) did not have adequate dilation to complete the D&E on day 2. One day of overnight dilators with or without adjuvant pharmacologic therapy is sufficient for most D&Es in this gestational range.

6. *Is there evidence to support use of misoprostol or mifepristone as an adjuvant to overnight osmotic dilators for D&E at 20–24 weeks' gestation?*

A randomized controlled trial by Drey and colleagues included 196 patients at 21–23 weeks' gestation who were randomized to receive 3–4 h of 400 mcg of buccal misoprostol versus placebo in addition to overnight laminaria [39]. The procedural duration in the laminaria-plus-misoprostol cohort was on average 1.7 min shorter than in the placebo group ($p = 0.02$), with slightly greater initial cervical dilation (75 mm vs. 73 mm, $p = 0.04$). However, the physicians did not find the D&Es to be subjectively easier, and the median procedural durations did not differ. Patients who received misoprostol reported significantly more pre-procedural pain than those receiving placebo (52% vs. 11%, $p < 0.001$).

In the multicenter randomized controlled trial by Goldberg and colleagues, patients between 16 and 23 6/7 weeks' gestation were randomized to one of three arms: overnight dilators alone, overnight dilators with 200 mg mifepristone, and overnight dilators with 400 mcg misoprostol given approximately 3 h preoperatively [38]. This trial included an early cohort (152 participants at 16–18 6/7 weeks) and a late cohort (148 participants at 19–23 6/7 weeks), all of whom initially received a mix of Dilapan-S® and 4 mm laminaria based on provider preference. The primary outcome of operative time—defined as placement of the first instrument in the uterus to removal of the last instrument—did not differ among the three arms in either gestational cohort. By contrast, a shorter total procedure time (speculum in to speculum out) was noted with adjuvant mifepristone in the later cohort, which was largely due to less time managing postoperative bleeding and complications. In addition, the D&Es in the mifepristone arm were subjectively easier, had a trend toward fewer complications (compared with the dilators-alone arm), and resulted in fewer side effects than in the misoprostol arm. However, the study was not powered to evaluate complications. Although complications did not differ significantly across groups, the frequency of complications with dilators alone (10%, 95% CI 4.2–16.0) was higher than with adjuvant misoprostol (2%, 95% CI 0–4.7) or adjuvant mifepristone (2%, 95% CI 0–4.8). Patients who received misoprostol had significantly more pain, fever, and chills.

In a recently published systematic review and meta-analysis, Cahill and colleagues evaluated the effect of adjuvant misoprostol with overnight dilators for D&E after 16 weeks [40]. Only three studies met inclusion criteria, including the two studies described above [38,39]. (The third study only included patients at 16–20 weeks of gestation.) The Cahill review shows that based on current evidence adjunctive misoprostol with osmotic dilators after 16 weeks does not significantly shorten procedure time or decrease need for mechanical dilation, but further research is needed to determine the effect of misoprostol on complications and blood loss.

No studies have shown increased bleeding, atony, or complications with adjunctive mifepristone for D&E after 20 weeks' gestation when used with osmotic dilators [37,38]. However, these studies did not have adequate power to find differences in complications or blood loss.

No data are available to define the most effective interval between mifepristone and the D&E procedure at 20–24 weeks' gestation. However, Casey and colleagues' randomized controlled trial among patients undergoing same-day termination between 14 and 19 6/7 weeks' gestation suggested that 4–6 h was insufficient for mifepristone to improve cervical ripening [41]. Their participants had cervical ripening with misoprostol and either mifepristone or placebo administered 4–6 h before D&E, with no significant difference in procedure times or initial cervical dilation with the addition of mifepristone.

As noted in the study by Goldberg and colleagues, approximately 18–24 h of preparation with mifepristone 200 mg and osmotic dilators the day before D&E was sufficient to make procedures significantly easier and faster, when measuring total procedure time from speculum placement to removal of all instruments from the vagina [38]. This trial suggests that 18–24 h is sufficient to achieve adjuvant mifepristone's cervical ripening effects in patients at gestational ages of up to 23 6/7 weeks. At the time of publication, the authors are not aware of data describing longer intervals of mifepristone use at this gestation.

In summary, adjuvant mifepristone for D&E at 20–24 weeks' gestation has been shown to decrease procedure time and improve providers' sense of ease of procedure without increasing side effects. Based on individual study data, adjuvant misoprostol may increase initial dilation and shorten procedure time slightly; however, a recent meta-analysis [40] shows no benefit to using adjuvant misoprostol in terms of bleeding or procedure time and that it is associated with increased patient side effects.

7. *Does prior hysterotomy increase risks of cervical preparation before D&E at 20–24 weeks' gestation?*

Prior cesarean delivery has been described as an independent risk factor for adverse events during D&E in general [42]. A case report of uterine rupture after overnight laminaria and two doses of 400 mcg misoprostol before a planned 23-week D&E in a patient with two previous cesarean deliveries suggests a possible elevation in risk [43]. However, little prospective data demonstrate that patients with a uterine scar have an increased risk of uterine complications after using osmotic dilators with adjuvant misoprostol as cervical preparation for D&E. A large retrospective study of D&Es using buccal misoprostol alone or in conjunction with laminaria between 12 and 23 6/7 weeks' gestation ($N = 2218$, 19% of which were at ≥20 weeks) found that patients with a history of cesarean birth were three times as likely as those without such a history to experience an adverse event (OR 3.11, 95% CI 1.14–7.98), of which none were uterine rupture or scar dehiscence. The study did not identify which specific adverse events occurred among those with or without a history of prior cesarean. The adverse events included cervical laceration; spontaneous rupture of membranes pre-procedure; spontaneous delivery of placenta or fetus before D&E; hemorrhage; fever, fainting, nausea or vomiting; incomplete dilation, suspected perforation; incomplete abortion; and sepsis [44]. In the labor induction literature, providers often use misoprostol by itself or in conjunction with mifepristone (without osmotic dilators) without an elevated risk of cesarean

scar dehiscence or rupture at 20–24 weeks' gestation among pateints with one prior cesarean [45]. Patients with a uterine scar undergoing D&E at 20–24 weeks' gestation are at elevated risk of adverse events, but no data exist to attribute the elevated risk to cervical preparation.

8. *Does evidence support the use of same-day cervical preparation at 20–24 weeks' gestation?*

Some evidence supports the use of same-day misoprostol as cervical preparation at 20 weeks' gestation and possibly later. A case series of patients undergoing same-day cervical preparation before D&E included 229 patients at 20 weeks' gestation and an additional 17 patients at 21–23 weeks' gestation [46]. None of the patients had had a prior cesarean. All patients received a loading dose of 200–600 mcg misoprostol, with dose and route (vaginal vs. buccal) dependent on the provider. Additional doses of misoprostol were given every 2 h after examination. Patients received an average of 3 doses of misoprostol (range 1–5). The median time from administration of buccal misoprostol until D&E completion was approximately 5 h. One cervical laceration occurred at 20 weeks, with no complications in the subset of patients at 21–23 weeks' gestation. However, given the study design and small numbers, we cannot draw conclusions about operative time, procedure difficulty, complications, or patient satisfaction, especially at gestations of more than 20 weeks.

In a review of D&Es done by the British Pregnancy Advisory Service, Lyus and colleagues [47] describe D&Es completed at 18–21 6/7 weeks' gestation using 400 mcg vaginal misoprostol and 1–3 synthetic dilators for an average of 3 h and 40 min before the D&E. The cohort included 274 patients at an average of 20 weeks' gestation, none of whom required mechanical dilation. The four experienced providers who completed all the procedures had only two immediate complications: a cervical laceration requiring suture and a fetal expulsion before D&E.

In 2007, a retrospective study published by Poon and colleagues [34] described cervical preparation practices of abortion providers at King's College Hospital in the UK. Their initial same-day protocol for cervical preparation through 23 6/7 weeks' gestation utilized one or two Dilapan and up to 800 mcg vaginal misoprostol, with the D&E procedure completed 4–7 h later. Of the 34 patients who received this protocol, six patients (18%) required no further dilation and the remaining 28 required mechanical dilation. Three patients had cervical damage requiring repair, and two patients had heavy bleeding requiring an overnight stay.

Some evidence shows the feasibility of same-day cervical preparation before D&E at 20–24 weeks' gestation, but only experienced providers should offer these procedures. Further studies should evaluate safety, procedure time, complications, patient acceptability, and ideally, any long-term sequelae of same-day D&Es at gestations of more than 20 weeks.

9. *Does evidence support use of mifepristone alone or mifepristone with misoprostol at 20–24 weeks' gestation without osmotic dilators?*

Shaw's randomized controlled trial of 75 patients receiving a D&E between 19 and 23 6/7 weeks' gestation randomized participants into three groups: overnight 200 mg mifepristone without dilators and 400 mcg buccal misoprostol on the day of surgery; overnight dilators with overnight mifepristone and misoprostol on the day of surgery; and overnight dilators with overnight placebo and misoprostol on the day of surgery [48] Procedure time was significantly longer ($p < 0.01$) in the mifepristone-misoprostol group without dilators (18.5 min) than in the group with dilators, mifepristone, and misoprostol (12 min) and the group with dilators, misoprostol, and placebo (13 min). They observed a nonstatistically significant difference in complications ($p = 0.20$) between the mifepristone-misoprostol group without dilators (2 perforations and 5 cervical lacerations) and the group with dilators, mifepristone and misoprostol (1 perforation); and the group with dilators, misoprostol, and placebo (1 cervical laceration). Of note, almost all complications (6 of 7) occurred during D&Es provided by gynecologists undergoing additional Family Planning training, while one perforation occurred during a procedure done by an attending surgeon. Based on this study, while overnight mifepristone plus same-day misoprostol without dilators may be feasible, the high frequency of observed complications is concerning. However, the study was not powered to assess complications.

Eliminating dilator use before procedures in the late second trimester is feasible and may decrease discomfort and dilator-related preoperative time for patients. However, procedure time is lengthened, complications may be more frequent and provider experience may affect risk. We have no information about potential impact on subsequent pregnancy outcomes.

4. Conclusions

Significant new research can help guide our cervical preparation choices. As of 2013, the majority of U.S. abortion providers used a combination of misoprostol and osmotic dilation before late second-trimester D&E, and numbers of dilators used and duration of use varies. Dilapan-S® requires a shorter time to achieve maximum dilation and may be more effective than laminaria for cervical preparation before late second-trimester D&E. One day of overnight dilators with or without adjuvant pharmacologic therapy is sufficient for most D&Es at 20–24 weeks' gestation. Current evidence supports the use of mifepristone as an adjuvant to osmotic dilators for D&E at 20–24 weeks' gestation. By contrast, procedure time appears to lengthen and complications increase when mifepristone and misoprostol are used without osmotic dilators at 20–24 weeks' gestation. Adjuvant mifepristone has been shown to decrease procedure time and improve providers sense of ease of procedure without increasing side effects for D&E at 20–24 weeks' gestation. Addition of misoprostol does not suggest benefit and causes more cramping and pain. Patientswith a uterine scar undergoing D&E at 20–24 weeks' gestation are at elevated risk of adverse events, but no data exist to attribute the increased risk to cervical preparation. While there is evidence that same-day cervical preparation before D&E at 20–24 weeks' gestation may be feasible, this practice should be limited to providers with significant experience with these regimens. Use of mifepristone and misoprostol alone without dilator use before procedures in the second trimester is possible, but procedure time is lengthened and complications may be more frequent.

5. Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Cervical preparation always should be used before D&E at 20–24 weeks' gestation to reduce D&E risks, including cervical laceration and hemorrhage.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- One day of overnight osmotic dilators, with or without adjuvant pharmacologic therapy, is sufficient to be able to complete most D&Es at 20–24 weeks' gestation.

- Dilapan-S® requires a shorter time to achieve maximum dilation and may be more effective than laminaria for cervical preparation before second-trimester D&E.
- Adjuvant mifepristone should be considered, because it makes D&Es subjectively easier at 20–24 weeks' gestation without adding side effects.
- Using mifepristone and misoprostol without osmotic dilators at 20–24 weeks' gestation lengthens D&E procedure time and appears to increase immediate complications. Pharmacologic-only regimens without adjuvant osmotic dilators should not be implemented widely without further research supporting their use.
- Use of misoprostol for cervical preparation before D&E at 20–24 weeks' gestation does not increase the risk of uterine scar dehiscence.
- Adjuvant misoprostol for patients who received uncomplicated dilator insertions the day before D&E does not appear to significantly decrease procedure time or decrease need for initial dilation, and it increases side effects, such as pain, cramping, and nausea.
- Current retrospective data do not show an association between history of osmotic dilation before D&E and subsequent preterm birth.

The following recommendations are based primarily on consensus or expert opinion (Level C):

- Consider using more osmotic dilators as gestational duration advances.
- Some evidence shows the feasibility of same-day cervical preparation before D&E at 20–24 weeks' gestation with synthetic dilators plus adjunctive misoprostol or serial doses of misoprostol, but this should be limited to providers with significant experience with these regimens.

6. Recommendation for future research

Additional research is needed to address concerns about the association between abortion and subsequent preterm birth, especially to assess the effects of various cervical preparation regimens. Research on mifepristone has added significantly to the ability to provide safe, efficient cervical preparation before D&E. The use of mifepristone without osmotic dilators should be studied to offer more options to patients and decrease the need for a separate procedure to place osmotic dilators. Larger studies of risk and complications among subgroups associated with higher risk cervixes, such as nulliparas or younger patients, could be helpful in optimizing cervical preparation for these patients. While current data favor adjunctive mifepristone over misoprostol for cervical preparation, future research should evaluate whether misoprostol may be of benefit by increasing uterine tone and decreased bleeding.

7. Sources

MEDLINE and EMBASE databases were searched from 1966 to 2018. English-language abstracts were reviewed for relevance, with articles and contemporary chapters reviewed for any additional references. An automatic e-mail notification update was created on this topic to continue to review any new articles published during the course of preparing the guidelines. We excluded non-English articles.

8. Intended audience

This Society of Family Planning Clinical Recommendation was developed for its members and other clinicians who provide D&Es at 20–24 weeks' gestation or who care for patients undergoing these procedures. This recommendation may be of interest to other professional groups that set practice standards for family planning services. The purpose of this document is to review the medical literature evaluating common means of cervical preparation for D&Es at 20–24 weeks' gestation. This evidence-based review should guide clinicians in preparing the cervix before D&E, although it is not intended to dictate clinical care.

9. Authorship

These guidelines were prepared by Justin T. Diedrich, MD, MSCI; Eleanor A. Drey, MD, EdM; and Sara J. Newmann, MD, MPH; and were reviewed and approved by the Board of the Society of Family Planning.

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Original research article

Infection and extramural delivery with use of digoxin as a feticidal agent☆

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Abstract

Background: Many abortion providers use digoxin to induce fetal demise prior to dilation and evacuation (D&E). Our primary objective was to examine the frequency of infection and extramural delivery following digoxin use.
Study Design: We conducted a retrospective single-cohort study. Inclusion criteria were all women between 18 and 24 weeks of estimated gestational age who received digoxin in preparation for D&E at our outpatient facility. We queried two electronic databases to collect data on the frequency of extramural delivery and the rate of perioperative infection.
Results: From January 1, 2000, to December 31, 2008, 4906 abortions were performed between 18 and 24 weeks of estimated gestation with digoxin injection administered as feticidal agent 1 day prior to D&E. Extramural delivery frequency was 0.30%, and infection frequency was 0.04%. There were no significant differences in the frequency of extramural deliveries across procedure year (p=.2), estimated gestational age (p=.3), race/ethnicity (p=.2) or maternal age (p=.3).
Conclusion: Rates of extramural delivery and infection are acceptably low following digoxin use prior to scheduled D&E.
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Keywords: Digoxin; Extramural delivery; Infection; Dilation and evacuation

1. Introduction

The safety of induced abortion in the second trimester has been well established [1]. In the United States, dilation and evacuation (D&E) is the most common method of pregnancy termination beyond 13 weeks of estimated gestational age, with more than 140,000 procedures performed annually [2]. In recent years, the practice of inducing fetal demise prior to the procedure has become more common for a variety of reasons.

Passage of the Partial-Birth Abortion Ban Act of 2003 made it a violation to perform an abortion in which a "living fetus" is delivered vaginally "deliberately and intentionally" past certain anatomical landmarks, before fetal demise occurs [3]. When the law was upheld in 2007, many providers performing second-trimester abortion elected to use a feticidal agent to ensure that the law would not be violated because the fetus was no longer "living" when the procedure commenced.

There are several techniques that can be used for induction of fetal demise prior to a termination of pregnancy including cardiac puncture and exsanguination, air embolization and umbilical cord transection [4]. Currently, in the United States, pharmacologic agents are the most commonly used method [4].

For many years prior to the 2003 legislation, clinicians at our site had been using digoxin to facilitate second-trimester termination of pregnancy for other potential benefits. It is believed by some clinicians that digoxin injection results in softer, macerated fetal tissues that may ease evacuation of the fetus and potentially decrease procedure time and risk of complications [5,6]. Finally, research has shown that some patients prefer the induction of fetal demise prior to the abortion procedure [7].

Data on the side effect profile of digoxin, when used as a feticidal agent, are scarce. Other than extramural delivery, there have been no reports of complications associated with digoxin use for this indication. One study of eight women

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who received 1.0 mg of digoxin intra-amniotically showed no adverse maternal cardiovascular effects [8]. Another study evaluating digoxin doses of 0.125–1.0 mg administered either intra-amniotically or intrafetally supported its safety [9]. Only one study employed postinjection maternal electrocardiographic monitoring, during which no arrhythmias were noted [8].

In reference to the specific outcomes of infection and extramural delivery following digoxin injection, there is still a paucity of data. The only cases of infection documented in patients who received a feticidal injection were with the use of potassium chloride intrafunic, intracardiac and transcervically, respectively [10–12]. There are several case series that examine the rate of extramural delivery after iatrogenic fetal demise. Molaei et al. [9] specifically examined the safety of digoxin as an agent to induce fetal demise. In this series, there were 1796 cases, of which nine women who received a digoxin injection experienced spontaneous contractions and were sent to the hospital prior to the scheduled return visit (0.5%). Seven women had received intrafetal and two had received intra-amniotic digoxin [9].

In August of 2009, Dean et al. [13] published in abstract form only a retrospective double-cohort study consisting of 566 patients in cohort A who received digoxin prior to D&E and 513 patients in the control group, cohort B. They found that digoxin injection prior to D&E is associated with increased rates of spontaneous abortion (1.9% vs. 0%) and infection (1.2% vs. 0.2%) when compared to controls who did not receive digoxin. The purpose of conducting the current study was to add to the growing body of evidence evaluating digoxin's safety when used to induce fetal demise. We hypothesized that study subjects who were administered digoxin intrafetally or intra-amniotically would have a small absolute risk of extramural delivery and an infection frequency consistent with historical norms for the procedure itself.

2. Materials and methods

Our clinic uses an electronic practice management (EPM) system to track all procedures performed. Data collected includes patient demographics and estimated gestational age as obtained by ultrasound examination. We also maintain a second electronic database of all adverse events experienced by patients including, but not limited to, hospital transfers, out of office deliveries and postoperative infections requiring hospitalization or IV therapy. Collection and documentation of these events are by clinic staff or providers from outside institutions reporting on our patients presenting to them for care. These reports are collected contemporaneously with each event.

Multiple prior internal quality-assurance studies have been completed as process measures to ensure that these databases are reliable and usable sources of information. One hundred fifteen charts were randomly selected from six sites to analyze whether the gestational age determined by ultrasound examination and documented by the clinician at the time of the procedure matched what was recorded in the EPM system. All gestational ages reported by the database matched the information in the charts to within 1 week. Our adverse event database was verified by a separate audit of 100 randomly selected charts. We reviewed all charts for any documentation of infection defined as temperature greater than or equal to 100.4°F, clinical suspicion of infection, treatment with an antibiotic other than doxycycline or metronidazole (which are given as routine prophylaxis) or transfer to a hospital. There were no cases that met infection-defining criteria identified by the chart review, which accurately corresponded to our adverse event database.

We searched our EPM system for all abortion procedures between 18 and 24 weeks of estimated gestational age and retrieved demographic information on these women. We then searched our adverse event database to identify patients who met our inclusion criteria. The aforementioned electronic databases were queried using the SQL Server .05 for CPT code 59841 to obtain a list of all surgical abortions performed from January 1, 2000, to December 31, 2008. We then searched within that list for all patients who received digoxin by using code x6082. All women included in the study were between 18 and 24 weeks of estimated gestational age, and all received 1.0 mg digoxin per clinic protocol, injected either intra-amniotically or intrafetally shortly after laminaria placement 1 day prior to the D&E procedure. Digoxin was used for abortions performed between 18–20 weeks of gestation only from May 2007 to August 2008. While the clinic protocol utilized digoxin injection for all procedures performed at 20 weeks or greater since 1999, the starting gestational age was decreased to 18 weeks in response to the Partial Birth Abortion Act, which became effective in 2007. Digoxin use for the 18–20-week gestational age was discontinued in August 2008 secondary to two out-of-office deliveries in this earlier gestational age group.

We abstracted maternal age, estimated gestational age, race, ethnicity, procedure date, occurrence of infection and occurrence of extramural delivery from our databases. The following maternal age categories were employed in analysis: 0–12, 13–15, 16–20, 21–25, 26–30, 31–35, 36–40, 41–45 and 46+. Race and ethnicity were combined into a single race/ethnicity variable by categorizing any subject with Hispanic ethnicity as Hispanic and all non-Hispanics as Asian/Pacific Islander, Black, Native American/Alaskan Native, White or other/unknown. We calculated annual, race-specific, age-specific, estimated-gestational-age-specific and overall frequencies of extramural deliveries. Since only two infectious complications occurred over the study period, we were unable to perform stratified analysis for infections. Infection rates were compared to published historical norms (ranging from 0.05% to 2.00%) following second-trimester abortion [14]. We calculated exact binomial 95% confidence intervals (CIs). The presence of differences in event frequencies across age group, race/ethnicity and

year was assessed with the Fisher's Exact Test. Linear trends in event frequency across time and gestational age were evaluated by visual inspection and Poisson regression. Statistical analysis was carried out using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and Excel 2003 (Microsoft Corp., Redmond, WA, USA).

Institutional Review Board approval was obtained from Independent Review Committee located in San Anselmo, CA.

3. Results

Between 2000 and 2008, there were 4906 D&Es performed after digoxin was administered. Characteristics of the patients who underwent this procedure are shown in Table 1. Of these patients, 12 experienced definite extramural deliveries. An additional three patients failed to return after laminaria placement and, despite rigorous attempts to contact them, were subsequently lost to follow-up. Assuming these three patients did go into spontaneous labor, at most 15 women experienced extramural deliveries (0.3%, 95% CI 0.2–0.5), and two patients had a perioperative infection (0.04%, 95% CI 0.0–0.2). One patient was a 19-year-old with a history of one prior cesarean section who presented in December of 2002 at 22 weeks of estimated gestation for a D&E and was administered digoxin per protocol. On the second day after her uncomplicated D&E procedure, she called the clinic stating her temperature was 102.9. She was referred to the nearest hospital emergency department where she was admitted, treated with intravenous antibiotics and recovered completely. The second patient was a 17-year-old at 20 weeks of estimated gestation who presented on the day of her procedure complaining of fevers and chills. Her heart rate was in the 120s, and her temperature prior to D&E was 100.4. She had an uncomplicated procedure and was treated with ceftriaxone postoperatively.

The frequency of extramural delivery by year of the procedure, estimated gestational age and race/ethnicity is shown in Table 2. There were no significant differences in the frequency of extramural deliveries across procedure year (p=.2) (Fig. 1), estimated gestational age (p=.3),

Table 1
Characteristics of individuals who received D&E with digoxin injection between gestational weeks 18 and 24 from 2000 to 2008 (n=4906)

Characteristic	n (%)
Age group, years	
13–15	142 (2.9)
16–20	1784 (36.4)
21–25	1565 (31.9)
26–30	701 (14.3)
31–35	409 (8.3)
36–40	238 (4.9)
41–45	62 (1.3)
46+	5 (0.1)
Race/ethnicity	
Asian/Pacific Islander	295 (6.0)
Black	866 (17.7)
Hispanic	2479 (50.5)
Native American/Alaskan Native	31 (0.6)
White	807 (16.5)
Other/unknown	428 (8.7)
Year	
2000	349 (7.1)
2001	269 (5.5)
2002	306 (6.2)
2003	326 (6.6)
2004	451 (9.2)
2005	784 (16.0)
2006	674 (13.7)
2007	900 (18.3)
2008	847 (17.3)
Gestational week	
18	148 (3.0)
19	194 (4.0)
20	1077 (22.0)
21	1189 (24.2)
22	1062 (21.7)
23	929 (18.9)
24	307 (6.3)

Table 2
Frequency of extramural delivery of subjects who received digoxin injection prior to D&E by year, estimated gestational age and race (n=4906)

	Procedures	Extramural deliveries	Frequency of extramural delivery, percentage (95% CI)
Year			
2000	345	4	1.2 (0.3–3.0)
2001	269	0	0 (0–1.4)
2002	306	0	0 (0–1.2)
2003	324	2	0.6 (0.1–2.2)
2004	451	0	0 (0–0.8)
2005	784	2	0.3 (0–0.9)
2006	674	1	0.1 (0–0.8)
2007	900	3	0.3 (0.1–1.0)
2008	847	3	0.4 (0.1–1.0)
Gestational age, weeks			
18	148	2	1.3 (0.2–4.8)
19	194	0	0 (0–1.9)
20	1077	3	0.3 (0.1–0.8)
21	1189	3	0.3 (0.1–0.7)
22	1062	2	0.2 (0–0.7)
23	929	3	0.3 (0.1–0.9)
24	307	2	0.7 (0.1–2.3)
Race/ethnicity			
Asian	295	3	1.0 (0.2–2.9)
Black	866	2	0.2 (0–0.8)
Hispanic	2472	7	0.3 (0.1–0.6)
American Indian/ Alaskan Native	31	0	0.3 (0–11.2)
White	807	2	0.2 (0–0.9)
Other	427	1	0.3 (0–1.3)
Total	4,906	15	0.3 (0.2–0.5)

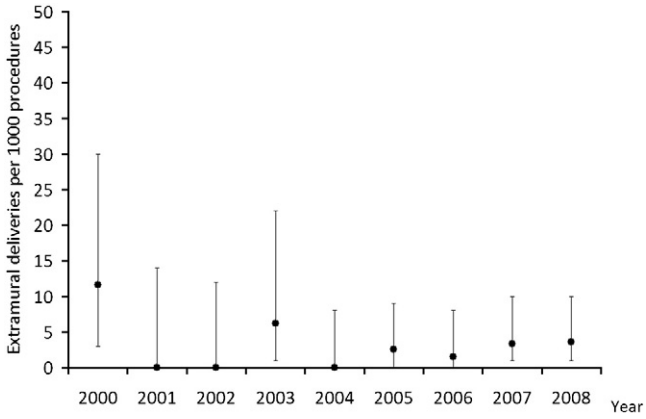

Fig. 1. Frequency of extramural deliveries per 1000 procedures (·) and 95% CIs (I).

race/ethnicity (p=.2) or maternal age (p=.3). No secular trends in frequency of extramural deliveries were apparent (p for linear trend=.2), nor was there a significant linear trend in the frequency of extramural delivery for increasing gestational age (p for trend=.9).

4. Discussion

These results are reassuring in regards to patient safety. For practitioners who wish to achieve fetal demise prior to performing a D&E procedure, this study shows that use of digoxin does not cause maternal adverse events in the vast majority of cases. Because digoxin injection may confer a small additional risk of extramural delivery beyond that inherent in the D&E procedure itself, the possibility should be addressed with patients. This discussion should include an individualized plan of where to present should labor begin at home. If, however, the injection has been effective at inducing fetal demise, care is often facilitated more smoothly at outside institutions by eliminating the debate of whether to resuscitate a periviable fetus.

There are many limitations to our study. Unfortunately, our EPM system was initiated shortly before our use of digoxin, and, as a result, we have no appropriate comparison group. In addition, although we have data for patients undergoing procedures from 18 to 24 weeks of estimated gestational age, our facility only administered digoxin prior to 20 weeks for a short time (May 2007 to August 2008). As mentioned previously, this practice was discontinued secondary to two out-of-office deliveries in this earlier gestational age group. As expected, secondary to the small number of patients in this estimated gestational age range, the two out-of-office deliveries did not reach a statistically significant difference from prior years where its use was performed only for more than 20 weeks of estimated gestational age.

Our study is also limited by our electronic databases. Demographic data were obtained from our EPM system, which was originally intended for billing purposes only. Ideally, we would have preferred to look for an association of extramural delivery with gravidity and parity. Unfortunately, these clinical data are not easily obtained using the current EPM system.

Our study has many strengths. To verify our results, we used multiple process measures to ensure our data collection was accurate. Though we are dependent upon outside institutions reporting back to us when our patients present for care with clinical signs of infection, this communication occurs with great regularity for other complications not included in this study. In addition, though there is a possibility that our infection rate is an underestimation; the cases that we may have missed are likely postoperative rather than a result of the digoxin injection. Any patient infected by the injection itself would likely have had clinical signs or symptoms 1 day later upon presentation for the D&E. We are confident that our occurrence log captured all cases of out-of-office delivery because our staff employ rigorous means to contact all patients who have previously undergone laminaria placement and digoxin injection.

The question remains as to why our data differ from those reported by Dean et al. [13]. Our rates of extramural delivery and infection are similar to the control group in their study. Possible explanations for the difference include variations in digoxin injection technique, variations in cervical preparation technique, underlying differences in population characteristics, sample size and variations in procedure length (i.e., 1 vs. 2 days of cervical preparation prior to D&E procedure). In addition, definition of "spontaneous abortion" in our study is an "out-of-office delivery" as opposed to the inclusion by Dean et al. of patients who delivered in the office prior to their procedure. Unfortunately, data on the rate of extramural delivery following preparation for D&E consisting of laminaria alone (no digoxin) have not been published.

It is possible that any subclinical infection that may result from digoxin administration would be treated with the doxycycline that is routinely used prior to any D&E procedure. To date, there is insufficient data to determine whether second-trimester abortion is made safer by using digoxin to induce fetal demise prior to the procedure. To justify the potential increase in spontaneous labor and out-of-office delivery, an increase in safety would seem warranted. The induction of fetal demise remains largely a decision based on practitioner and patient preference. However, for those providers who choose to employ the technique, these data add to the growing body of literature that supports the minimal risk inherent in digoxin injection when used as a feticidal agent.

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