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# Transvaginal administration of intraamniotic digoxin prior to dilation and evacuation

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## Abstract

**Background:** Transabdominal injection of digoxin into the amniotic fluid or fetus to induce fetal demise before dilation and evacuation (D&E) abortion has become common practice since the passage of the Partial-Birth Abortion Ban Act in 2007.

**Study Design:** We performed a prospective study to assess the feasibility of transvaginal administration of intraamniotic digoxin the day before D&E. All women between 18 0/7 and 23 5/7 weeks of gestation seeking termination from December 2009 to May 2011 were approached for study participation. Women who declined participation were asked to identify their primary rationale. For women declining study participation, transection of the umbilical cord during D&E was performed to meet the requirements of the ban.

**Results:** Over 18 months, 134 women met study entry criteria and 108 (81%) declined to participate. Of the 26 women who enrolled, 1.0 mg undiluted digoxin was successfully administered transvaginally in 24 (92%, 95% confidence interval 75%–99%). The most common reasons for declining participation were discomfort with preoperatively inducing fetal demise (37%) and desire to avoid a medically unnecessary medication (36%).

**Conclusions:** Transvaginal administration of digoxin is a feasible alternative to transabdominal administration to induce preoperative fetal demise. The majority of women decline digoxin administration when an alternative is available.

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**Keywords:** Digoxin; Dilation and evacuation; Transvaginal; Abortion; Fetal demise

## 1. Introduction

Passage of the Partial-Birth Abortion (PBA) Ban Act in 2007 resulted in a change in US abortion practice for legal reasons without medical indication. Induction of fetal demise before dilation and evacuation (D&E) has become common practice [1–6]. The reasons most frequently cited for this practice are avoiding prosecution, facilitation of D&E abortion, patient preference and avoiding extramural abortion with signs of life [2–5].

Induction of fetal demise before D&E typically involves transabdominal injection of a cardiotoxic drug, digoxin or

potassium chloride, into the amniotic fluid or fetus before uterine evacuation [3]. Currently, there is no standard of care for preoperative induction of fetal demise. Many providers believe that by inducing and documenting fetal demise prior to abortion, they will avoid any potential accusations of intending to violate the law [2,3]. However, this procedure before D&E is not required to comply with the PBA Ban as other options are available including transection of the umbilical cord during the D&E procedure [2,3].

When preoperative induction of fetal demise is performed, it is most commonly done by transabdominal approach under ultrasound guidance for drug delivery [1,6–10]. A transabdominal approach can be uncomfortable for the patient, may increase patient anxiety as the needle is in plain sight, and can be technically difficult for the physician to accomplish, especially in obese patients. For patients undergoing genetic

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testing in pregnancy, transabdominal amniocentesis or chorionic villus sampling (CVS) is associated with more pain as compared to transcervical CVS [11]. For providers, transabdominal approaches can be more difficult in obese women [12]. Transcervical CVS appears to have the same infection risk as amniocentesis [13].

Transvaginal administration of cardiotoxic drugs for induction of fetal demise prior to D&E may offer several advantages over transabdominal drug administration for both patients and providers. Since the vagina and cervix are already being accessed for dilator placement, a transcervical or transvaginal approach may decrease patient anxiety and pain without adding significant procedure time as compared to a transabdominal approach. We hypothesized that digoxin can be easily administered transvaginally to induce preoperative fetal demise prior to D&E and that the procedure would be well tolerated by subjects.

## 2. Methods

We performed a prospective study to assess the feasibility of transvaginal administration of intraamniotic digoxin (1.0 mg) with ultrasound guidance immediately before osmotic dilator placement, 1 day prior to D&E. Transection of the umbilical cord during D&E was the institution's standard procedure to meet the requirements of the PBA Ban Act. As a secondary objective, women who declined participation were asked to identify their primary reason for not participating. The trial was approved by the University of Pittsburgh Institutional Review Board and performed at Magee-Womens Hospital of the University of Pittsburgh Medical Center.

### 2.1. Eligibility and enrollment

Healthy women aged 18 years and older at 18 0/7 to 23 5/7 weeks of estimated gestational age with singleton pregnancies who were seeking D&E for pregnancy termination from December 2009 to May 2011 through the faculty practice and the resident clinic were offered participation. Enrollment in the study occurred immediately before dilator placement, usually 1 day prior to the scheduled D&E. Women were excluded from study participation if they had a contraindication to digoxin, including personal history of cardiac disease, current use of digoxin, personal history of chronic renal failure, or allergy to or intolerance of digoxin. Women with spontaneous fetal demise, suspicion or diagnosis of intraamniotic infection at enrollment, suspicion or diagnosis of cervicitis, spontaneous rupture of membranes prior to dilator placement, oligohydramnios or anhydramnios on any evaluation before procedure, an urgent need for D&E, prior participation in this research study or current participation in another research study that would interfere with the conduct of this study were also excluded.

If a woman declined study participation, the physician obtained verbal consent to ask her why she did not want to

participate and recorded her response on a de-identified data sheet. Responses were organized by issues related to study participation (not wanting to participate in a study, confidentiality concerns), issues related to digoxin administration (fear of pain, discomfort with preoperatively inducing fetal demise, fear of precipitating labor or rupture of membranes, exposure to unnecessary medication) or "other," which provided a blank line for write-in comments. Basic demographic information (age, gravidity, parity, gestational age and reason for abortion) was also collected.

### 2.2. Intervention

Each participant was asked to empty her bladder immediately before osmotic dilator placement. A physician investigator performed a brief abdominal ultrasound to subjectively confirm normal amniotic fluid levels, the presence of fetal cardiac activity and an empty bladder. Any participant with oligohydramnios or anhydramnios, and/or fetal demise was excluded from further study participation. The ultrasound was not visible to study subjects.

A bimanual exam was performed to evaluate for clinical signs of infection. A speculum was then placed in the vagina, the cervix was cleansed, a cervical anesthetic block was administered with 10 mL of 1% lidocaine with approximately 5 mL at 3 o'clock and 5 mL at 9 o'clock, and a single-tooth tenaculum was placed on the anterior cervix as per the standard of care for dilator placement at our institution. After tenaculum placement, a physician investigator transvaginally placed a Cook Echotip® amniocentesis needle attached to a 10-mL syringe containing 1.0 mg undiluted digoxin (4 mL). The first 10 injections were all performed by the principal investigator (A.M.G.), who refined techniques before involving other co-investigators. Depending on the participants' anatomy, the needle was placed at the junction of the anterior cervicovaginal fold, the anterior vagina below the anterior speculum blade or through the anterior cervical stroma. The injecting physician advanced the needle until withdrawal of the syringe plunger yielded amniotic fluid confirming intraamniotic placement. If blood was obtained, the injecting physician adjusted the needle placement before withdrawing again. Needle insertion was concurrently monitored via ultrasound by both the injecting physician and the physician performing ultrasound. Once correct placement was confirmed, the digoxin was injected. After completing the injection, the physician placed a ring forceps on the needle flush with the vagina or cervix to mark needle depth. The needle was withdrawn, and the depth of the injection was measured. The length of time starting when the needle touched the cervicovaginal mucosa and ending when the needle was completely withdrawn was recorded. Thereafter, the osmotic dilators were placed per standard of care.

Participants completed visual analog scales (VAS) [14,15] to assess pain immediately after tenaculum, immediately after digoxin administration and immediately

after dilator insertion was completed but before speculum removal. The VAS consisted of a 100-mm line where 0 mm equaled *no pain* and 100 mm equaled *severe pain*. At each assessment, subjects were asked to mark an ‘X’ along the line representing the amount of pain experienced. After completion of the procedure, the injecting physician ranked the ease of successfully placing the needle into the amniotic sac with possible responses of “very easy,” “easy,” “neutral,” “difficult” and “very difficult.” As part of usual standard of care, all participants received prophylactic oral antibiotics (doxycycline 200 mg) to be taken the night before the D&E procedure [16].

Each participant returned the following day for her scheduled D&E procedure. Information about any problems that occurred after dilator placement, with specific focus on rupture of membranes, infection, extramural delivery and need for admission, was obtained from the participant. If needed, medical records related to any complications or medical problems after digoxin administration were obtained. In the operating room at the start of the D&E procedure, abdominal ultrasound examination was performed to assess fetal cardiac activity.

One week after D&E, participants completed a scheduled phone follow-up and were asked if they experienced any signs, symptoms, or treatments for infection or other complications after the D&E procedure. If the subject could not be contacted by day 14, a certified letter indicating her need to contact the research office was sent. Participants were reimbursed \$35 for study participation.

### 2.3. Sample size

Our a priori hypothesis was that this method should be successful for at least 90% of women. We calculated that a sample size of 80 women would give a lower 95% confidence interval (CI) no less than 81%, which is 10% lower than the hypothesized efficacy rate for successful intraamniotic digoxin placement (95% CI 81%–96%). Based on surgical volumes, we anticipated that enrollment would take 6 months. As the study progressed and a substantial number of women declined participation, we established 18 months as the stopping point for enrollment.

### 2.4. Statistical analysis

Statistical analysis was performed using Stata 10 (StataCorp LP, College Station, TX, USA) and consisted primarily of descriptive analyses. Pain scores at the time of placement of tenaculum, transvaginal digoxin and dilator placement were analyzed by the Wilcoxon signed rank test. We compared the demographic characteristics, including reason for abortion, among women who accepted and those who did not accept study participation. Demographic variables were assessed using summary statistics. Continuous data were evaluated by the Student’s *t* test. Nonparametric data were assessed by Pearson  $\chi^2$  and Mann–Whitney *U* tests.

## 3. Results

Between December 2009 and May 2011, 134 women were invited to participate, with only 26 (19%) women agreeing to participate. All 108 women who declined to participate in the study gave verbal consent to collect information on their reason for declining. Women who declined participation were similar to women who accepted participation in age, estimated gestational age, gravidity, parity and number of prior abortions (Table 1). Women with a pregnancy affected by chromosomal or congenital anomalies were less likely to enroll than women with an undesired pregnancy or a pregnancy resulting from rape (relative risk= 0.3, 95% CI 0.1–0.9, *p*=.02). Women who declined study participation reported discomfort with preoperatively inducing fetal demise (*n*=40, 37%), desire to avoid an unnecessary medication (*n*=39, 36%), fear of pain (*n*=15, 14%), disinterest in participating in a research study (*n*=13, 12%), and fear of labor or rupture of membranes (*n*=1, 1%) as their primary reasons (Table 2).

Of the 26 women who accepted study participation, transvaginal intraamniotic digoxin administration was successful in 24 participants (92%, 95% CI 75%–99%). The first failed attempt was a 20-year-old G2P1 with an undesired pregnancy at 23 0/7 weeks of gestation who had a body mass index (BMI) of 48 and a history of one prior cesarean section. The procedure was attempted for 34 s of total time with a total needle depth of 10 cm. The physician rated the procedure as very difficult. The second failure was a 42-year-old G3P1 at 21 1/7 weeks of

Table 1  
Demographic characteristics of participants and nonparticipants

	Digoxin declined <i>n</i> =108	Digoxin accepted <i>n</i> =26	<i>p</i> value
Age, years	27.8±6.5	26.8±7.2	.50
Gestational age, weeks	21.1 (18.0–23.7)	20.9 (18.9–23.8)	.71
Gravidity	2.0 (1–13)	3.0 (1–9)	.12
Primigravida	25 (23%)	2 (8%)	.1
Multigravida	83 (77%)	24 (92%)	
Parity	1.0 (0–6)	1.5 (0–6)	.8
Nullipara	35 (32%)	5 (19%)	.24
Multipara	73 (68%)	21 (81%)	
Prior abortions	0 (0–6)	0 (0–1)	.54
None	76 (70%)	19 (73%)	.99
One or more	32 (30%)	7 (27%)	
Reason for abortion			
Undesired pregnancy	61 (56%)	22 (84%)	.07
Congenital	25 (23%)	2 (8%)	
Chromosomal	19 (18%)	2 (8%)	
Rape	3 (3%)	0	
Combined reasons for abortion			
Undesired/rape	64 (59%)	22 (84%)	.02
Congenital/chromosomal anomalies	44 (41%)	4 (15%)	

Data presented are mean±standard deviation, median (range) or number (percentage).

Percentages may not add up to 100 due to rounding.

Table 2  
Sample narratives from patients declining study participation

	Reason for abortion
I just want one more night with my baby.	Congenital anomaly
I don't want to walk around with a dead baby inside.	Chromosomal anomaly
I don't like the idea of not knowing when my baby died.	Chromosomal anomaly
I want the umbilical cord disconnected like would happen if the fetus was delivered in labor.	Congenital anomaly
I don't want any medicine that I don't have to have.	Undesired pregnancy
Why would I want something that I don't need?	Undesired pregnancy
I don't want another procedure.	Rape

gestation with a BMI of 34 and a history of one prior cesarean section. The fetus was vertex; three attempts were made for a total of 300 s without success. Neither needle depth nor physician assessment of difficulty was recorded for the second patient.

Of the 24 women with successful digoxin administration, most ( $n=22$ , 92%) were successful on the first attempt, and most ( $n=21$ , 88%) successful needle placements were at the anterior cervicovaginal fold. Digoxin was always delivered into the amnion; no intrafetal administrations were performed. The median time to accomplish digoxin administration was 40 s (range 15–206 s), and mean needle depth was  $7.25 \pm 2.4$  cm. Overall, physicians rated the ease of the procedure as easy (25%) or very easy (58%). Immediately after digoxin injection, 4 (17%) women reported cramping and 20 (83%) reported no side effects. There were no differences in pain scores, measured by VAS, when pain after tenaculum placement and pain after digoxin administration were compared (Wilcoxon signed rank test  $p=.16$ ). There were no complications with dilator insertion and no participant experienced premature rupture of membranes or extramural delivery.

On the day of D&E, all women who had received digoxin had ultrasound-confirmed fetal demise, which was assessed at 21–29 h (median 28 h) after digoxin administration. D&E was accomplished without complications in 23/24 (96%) of participants. One participant, a 24-year-old G7P5 with an undesired pregnancy at 20 1/7 weeks, history of four prior cesarean deliveries and BMI of 34 experienced a postabortal hemorrhage and was admitted to the hospital for overnight observation. She did not require a blood transfusion. She was discharged on postoperative day 1 in good condition.

Follow-up at 1 week was successful in 22/24 (92%) women; two participants noted events since the D&E. One participant was evaluated in the emergency room for carpal tunnel symptoms. One participant reported abdominal cramping, diarrhea and fever on postoperative day 3 that resolved spontaneously 1 day later. No other complications, including infection, were reported.

#### 4. Discussion

A transvaginal approach to deliver 1.0 mg intraamniotic digoxin is feasible, quick and well tolerated and successfully resulted in fetal demise in all participants who received the treatment. Women tolerated the procedure well, with 83% of participants reporting no side effects and only 17% ( $n=4$ ) reporting cramping immediately after digoxin delivery. There were no episodes of premature rupture of membranes or extramural delivery, and D&E was accomplished without complications in 96% of participants. The majority (83%) of physicians rated the procedure as easy or very easy.

Arguably, the most significant finding of our study is that the majority (81%) of women undergoing D&E during the 18-month enrollment period declined preoperative digoxin when it was not mandated and when an alternative method of inducing fetal demise was available. The reluctance to receive optional fetocidal digoxin found in this study differs from other reported experiences by providers [8,10]. Our study is the first to examine preoperative digoxin administration in a setting that does not mandate preoperative fetal demise and routinely performs an alternative method (transection of the umbilical cord at the time of D&E) in order to meet the requirement of the PBA Ban. Two previous studies of preoperative digoxin have reported that women prefer induction of fetal demise before D&E compared to fetal demise at the time of D&E [8,10]. However, standard protocol for inducing fetal demise at these two clinics frequently or routinely required digoxin prior to D&E; thus, women in these two studies did not generally have an alternative to receiving a fetocidal medication.

In the only randomized, placebo-controlled trial of preoperative digoxin before D&E, 126 women were enrolled, and 92% of participants in the digoxin and placebo arm (saline injection) reported a strong preference for fetal demise before abortion [8]. Among participants who said “they might want a digoxin injection for D&E in the future,” reasons included desire for fetal death before the procedure (35%) and belief that it made the procedure easier (29%) or less painful (19%) [8]. The authors also collected data on women who were eligible but declined study participation ( $n=52$ ). The most common reasons for declining participation were unwillingness to be randomized (35%), emotional upset or anxiety associated with the procedure (25%) and unspecified (27%) [8]. Notably, women who declined participation “had D&Es according to the standard protocol of the clinic, which in most cases included digoxin” [8]. Therefore, the population studied was likely a highly selected group that may not be representative of women seeking D&E because participants declining participation were also likely to receive digoxin and were unlikely to have an alternative such as transection of the umbilical cord at the time of D&E. Furthermore, women’s reported preference for preoperative fetal demise may have been based on the mistaken belief that digoxin is associated with an easier and less painful procedure, which was disproved in this same

trial [3,8]. The only other study to address patient preference for digoxin also recruited from an institution where digoxin was mandated by protocol for all second-trimester abortions [10].

This study, which was designed as a feasibility trial, taught us more about women and their preferences regarding fetal demise before D&E when choice is allowed throughout the procedure. Although we did not reach our sample goal of 80 women to determine feasibility, this trial was strengthened by the large sample size of women declining digoxin administration who were willing to describe their rationale. Because only 26 women accepted study participation and digoxin administration and there were a small number of participants ( $n=2$ ) that had unsuccessful digoxin attempts, we do not have enough information to be able to compare characteristics of women with successful versus unsuccessful attempts at transvaginal digoxin administration. However, when given an option of umbilical cord transaction as a means for physicians to meet the requirements of the PBA Ban, the majority of patients chose to decline digoxin administration.

Our study adds to prior research [1–3] that questions the motivation and necessity of preoperative administration of a feticidal agent prior to D&E. Because digoxin is not medically necessary or absolutely required to meet the requirements of the law, women's preferences should be considered when determining the necessity of preoperative feticide prior to D&E.

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