

Drugs used to induce fetal demise prior to abortion: a systematic review☆☆☆☆



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ABSTRACT

Clinicians have used fetidical agents prior to second trimester abortion for many years. Despite the widespread use of various agents to induce fetal demise, a comprehensive or systematic review of the evidence is lacking on the safety, effectiveness, and most effective routes of administration.

Objectives: To evaluate the existing drugs and routes of administration used in inducing fetal demise prior to abortion, and to determine the safety, effectiveness, and acceptability of these fetidical agents.

Methods: We searched PubMed, EMBASE, CINAHL, POPLINE, and Global Index Medicus to identify studies describing pharmacologic agents used to induce fetal demise prior to termination of pregnancy. We included randomized controlled trials and observational studies comparing digoxin, potassium chloride (KCL), and lidocaine to induce fetal demise. We included studies that evaluated the primary outcomes of safety and effectiveness, including success in achieving fetal demise, induction to expulsion time for medical abortion, dilation and evacuation time, as well as maternal side effects and complications. Two authors independently screened abstracts and full texts. One reviewer extracted data from the included studies, which was counterchecked by a second reviewer.

Results: We identified eight studies that met inclusion criteria: three randomized controlled trials, and five observational studies. A total of 4505 women received drugs to induce fetal demise at 17 to 38 weeks' gestation, including digoxin ($n = 4174$), KCL ($n = 324$), and lidocaine ($n = 7$). Intra-fetal digoxin was superior to intra-amniotic digoxin in achieving fetal demise (OR 3.51, 95% CI 1.60, 7.78). Intracardiac KCL 15% 2–3 mL reduced induction to expulsion time by 320 min ($p < .006$).

Similarly, intracardiac KCL 15% 1–3 ml reduced dilation and evacuation time from 16.1 ± 7.9 min to 12.7 ± 5 min ($p < 0.001$). Intracardiac lidocaine 2% 10 mL was more effective at achieving fetal demise than intracardiac KCL 6 mmol (85.7% vs. 57.9%). Intra-amniotic and intra-fetal digoxin 1 mg, as compared to no fetidical agent, led to greater pre-procedure expulsion, hospital readmission, and the presence of one or more signs of infection.

Conclusions: Evidence from included cohort studies demonstrates that digoxin, KCL, and lidocaine are all effective in inducing fetal demise. Intra-fetal administration of digoxin is superior to intra-amniotic digoxin administration. Administration of feticide using intracardiac KCL may shorten the abortion experience. Limited data from observational studies also supports an increase in maternal side effects and/or complications related to the administration of digoxin.

Implications: Intra-fetal administration of digoxin is more effective in achieving fetal demise when compared to intra-amniotic administration. There is a knowledge gap in determining the single best drug for inducing fetal demise prior to abortion. Additional research is needed to compare different fetidical agents in terms of safety and effectiveness.

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1. Introduction

Worldwide, approximately 73.3 million induced abortions occur each year [1]. Abortion can occur at any point during pregnancy, though restrictions are often placed on performing or obtaining an abortion at some point in pregnancy. There is a slight increase in morbidity and mortality associated with abortions as gestational age increases [2–5].

Clinicians have been using fetocidal agents prior to abortions for many years with the practice becoming more common [5–8]. There are several reasons providers induce fetal demise prior to abortion, including fears of legal retaliation; comfort of the patient, provider and/or other involved health care workers; the belief that dilation and evacuation (D&E) will be easier and faster; to avoid transient fetal survival after medical induction; and to avoid extramural delivery with signs of life [9–13].

Different agents have been employed to induce fetal demise. The most commonly used pharmacologic agents are digoxin, potassium chloride (KCL), and lidocaine. These agents are administered into the uterine cavity trans-cervically or abdominally.

These fetocidal agents can be injected into the amniotic fluid (digoxin), the fetal tissue (digoxin and lidocaine), or into the pericardium of the fetus (digoxin, KCL, and lidocaine). Despite the widespread use of these drugs to induce fetal demise, a comprehensive or systematic review of the evidence is lacking on their safety, effectiveness, and acceptability, as well as the most effective routes of administration. The objective of this review was to determine the effectiveness, safety, and acceptability of fetocidal agents, including various routes of administration. We specifically evaluated success in achieving fetal demise, abortion procedure/expulsion time, serious maternal adverse events, side effects, provider and patient acceptability of the procedure, and provider assessment of the difficulty of the surgical abortion procedure.

2. Materials and methods

We conducted this review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

2.1. Literature search

We searched PubMed, EMBASE, CINAHL, POPLINE, and Global Index Medicus using a combination of keywords related to drugs used in inducing fetal demise prior to abortion, including all studies published from the inception of each database to January 2020 (search strategy in Appendix). We limited the search to articles including human subjects. We applied no language restriction and we registered the review on PROSPERO.

2.2. Selection criteria

We included randomized control trials (RCTs) and observational studies with a comparison group reporting on any pharmaceutical fetocidal agent used prior to elective abortion. We included studies that evaluated both trans-cervical and trans-abdominal routes of administration and at least one of the following sites of injection: intra-amniotic, intra-fetal, and intracardiac. We excluded descriptive studies with no comparison group, case reports, editorials, opinion papers, or studies that included ectopic or molar pregnancy. We also excluded studies that assessed fetocidal agents for the purpose of reducing the number of fetuses in the pregnant uterus.

We included trials with primary outcomes of: success in achieving fetal demise, defined as no fetal cardiac activity following administration of the drugs, as identified prior to initiation of the abortion procedure and without restriction based on the timing of administration; and serious maternal complications (cardiac event, sepsis, pre-procedure delivery, uterine perforation, and uterine rupture). We also considered trials with secondary outcomes such as time to completion of the abortion (surgical procedure time to empty the uterus or induction time to complete fetal and placental expulsion), patient acceptability and/or satisfaction, provider acceptability and/or satisfaction, provider assessment of the difficulty of the procedure, and side effects (nausea, vomiting, diarrhea).

2.3. Study quality assessment and data synthesis

One researcher (TT) independently performed the data extraction and conducted a risk of bias assessment for all outcomes, per the Cochrane Handbook of Systematic Reviews of Interventions [15].

A second reviewer (CK) cross-checked this work. We performed a narrative synthesis for included studies. In cases where the randomized trials were sufficiently similar, we conducted a pooled analysis with meta-analysis statistical techniques to estimate the effect, using REVIEW MANAGER 5.3 (RevMan 2014). We used Mantel-Haenszel random effects meta-analysis for dichotomous outcomes and the chi-square (χ^2) test and *I*-square (I^2) statistic to compare between-study heterogeneity.

We used the Cochrane guideline risk of bias assessment tool [15] to assess the risk of bias for RCTs against six domains: selection bias (random sequence generation and allocation concealment), blinding of participants and personnel, blinding of outcomes assessment, attrition bias, reporting bias, and other sources of bias.

We conducted a risk of bias assessment for non-RCTs using ACROBAT-NRSi (a Cochrane risk of bias assessment tool for non-randomized studies of interventions).

3. Results

The search yielded 790 articles, eight of which are included in this review (Fig. 1). The articles include three RCTs and five observational cohort studies. One study was conducted in Taiwan [12] and one in Britain [16]. The other six studies were conducted in the United States of America (USA) (Table 1).

Across the studies, 4174 women received digoxin, 324 received KCL, and seven received lidocaine. Investigators described the administration site of these agents in four studies; they used either trans-abdominal or trans-cervical routes.

Providers identified three routes of injection across the studies including intra-amniotic, intra-fetal, and directly into the fetal cardiac space. Digoxin was administered into the intra-amniotic or intra-fetal space, while KCL and lidocaine were administered into the intracardiac space. The dose of digoxin varied from 0.125 to 3 mg. KCL dosing and concentration varied in three studies: 15% 1–3 mL, 2 mEq/mL 2–3 mL, and 6 mmol. Only one of the studies assessed the use of lidocaine 2% 10 mL injected into the intracardiac space. Study characteristics are described in Table 1.

Four studies compared intra-fetal vs. intra-amniotic injection of 0.125 to 3 mg digoxin [17–20]. Three studies compared feticide vs. no feticide; two of these studies used KCL 1–3 mL intracardiac [16,21] and one study used digoxin 1 mg intra-fetal [5]. The final study compared KCL 6 mmol intracardiac vs. lidocaine 2% of 10 mL intracardiac [12].

Among the eight studies, two studies evaluated feticide prior to medical abortion [12,21], while the rest described the use of feticide prior to dilation and evacuation. Participants' gestational ages ranged from 17 to 38 weeks.

The overall risk of bias for the RCTs was high, mainly due to the lack of blinding in outcome assessment and lack of blinding of the participants and personnel (Table 2 and Fig. 2). The risk of bias for the observational studies was also significant, mainly due to the lack of blinding and selection bias (Table 3).

3.1. Success in achieving fetal demise

Success in achieving fetal demise is defined as absence of fetal cardiac activity detected prior to abortion. Among the eight studies, five documented success in achieving fetal demise [12,17–20]. All five studies used ultrasound to evaluate fetal cardiac activity. Four of the five studies assessed fetal cardiac activity 24 h after administration of digoxin 0.125–3 mg intra-fetal vs. intra-amniotic (2 observational studies [17,19] and two RCTs [18,20]). The fifth study, an RCT comparing KCL

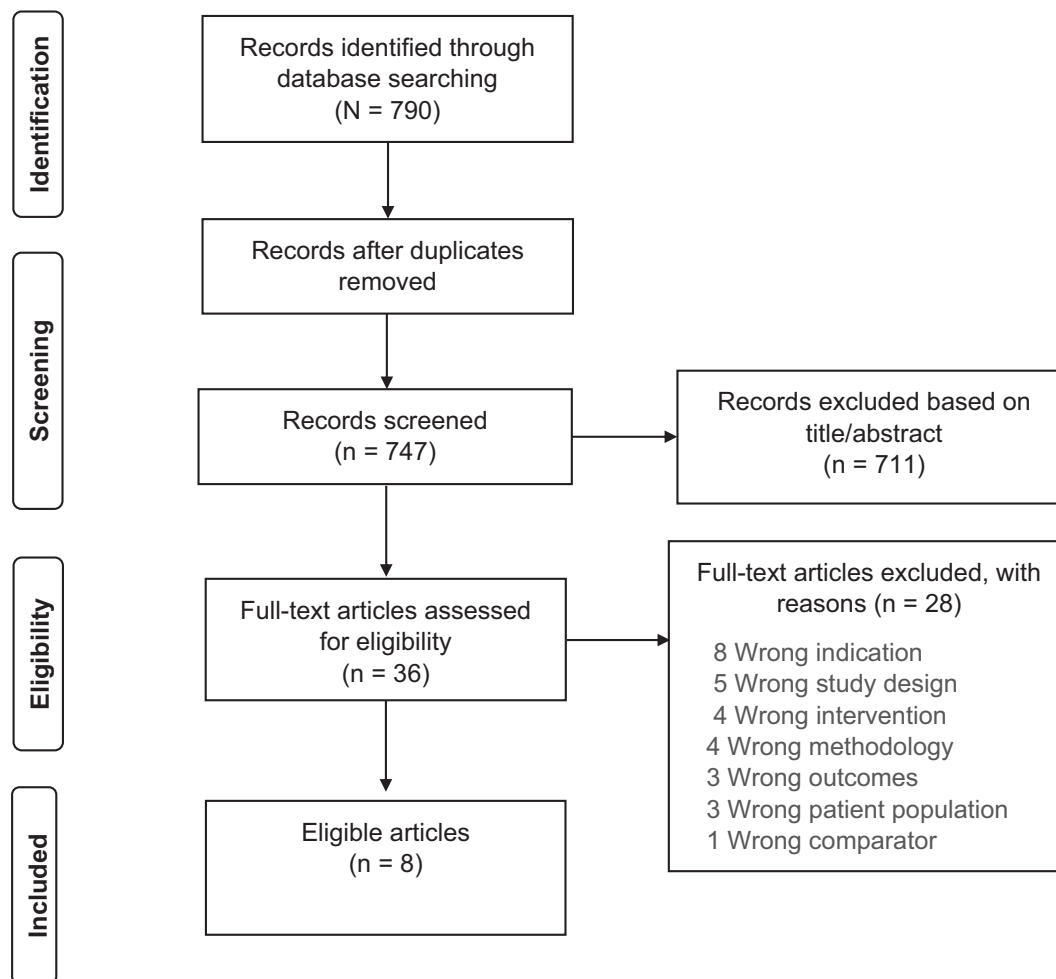


Fig. 1. PRISMA flow diagram showing studies included in the systematic review on drugs used to induce fetal demise prior to abortion.

6 mmol intracardiac vs. lidocaine 2% of 10 mL intracardiac, assessed fetal cardiac activity within 3 min following administration of the drug [12].

Pooled analysis of 2 RCTs [18,20] revealed that administration of digoxin 1–1.5 mg intra-fetal is superior in achieving fetal demise when compared to digoxin 1–1.5 mg intra-amniotic (OR 3.53, 95% CI 1.60, 7.78) (Fig. 3). Two observational studies [17,19] similarly showed a higher rate of success in the intra-fetal administration group. Tocce et al. [19] compared the success of digoxin at a dose of ≥ 1 mg vs. < 1 mg with all sites of administration and found that there is a higher rate of success at ≥ 1 mg dose ($p < .001$). Nucatola et al. [18] did not find a difference in success between 1 mg intra-amniotic and intra-fetal digoxin vs. 1.5 mg intraamniotic and intra-fetal digoxin ($p = .21$).

In the RCT comparing lidocaine 2% 10 mL intracardiac to KCL 6 mmol intracardiac, investigators found that administration of lidocaine is more effective at achieving fetal demise than KCL (85.7% vs. 57.9%) [12].

Providers in this study instilled normal saline (10–20 mL) into the pericardium to achieve fetal cardiac tamponade as a salvage mechanism in those subjects without cessation of fetal cardiac activity noted after 3 min, which increased the success rate to 100% in both groups.

3.2. Serious maternal adverse events

All studies except one [18] included serious maternal adverse events as an outcome throughout the follow-up period. Studies reporting serious maternal adverse events showed an overall higher rate of adverse events in patients receiving feticidal agents than those not receiving the medications. Dean et al. [5] compared D&E with or without digoxin for fetal demise and found more spontaneous abortion, infection, and

rehospitalization in the group receiving digoxin 1 mg intra-fetal or intra-amniotic ($p < .001$) (Table 4). A study by Lohr and colleagues on the other hand, compared D&E following induced fetal demise with intracardiac KCL 15% 1–3 mL vs. without feticide and found no difference in serious maternal complications between the groups (1% vs. 0.8%) [16]. When comparing medication abortion with 20 mg PGE2 every 4 h following intracardiac KCL 2 mEq/mL vs. without KCL, authors found no difference in the rate of elevated temperature more than 38 °C ($p = .89$) [21]. Two studies reported no serious maternal adverse events among.

patients receiving digoxin, KCL or lidocaine [12,17]. A study comparing digoxin 0.5–3 mg intra-amniotic vs. intra-fetal via trans-cervical injection reported the rate of major adverse events (extramural delivery, hemorrhage more than 500 cc, embolism, uterine perforation, hysterectomy, and hospitalizations) as 0.73% among 1665 women receiving digoxin [19].

3.3. Induction to expulsion time and procedure time

Two studies compared induction to expulsion or procedure time in two groups that received and did not receive feticidal agents [16,21]. Elimian et al. [21] reported medical induction using 20 mg PGE2 every 4 h until expulsion and showed shorter median expulsion time with those who received intracardiac KCL 2 mEq/ml 2–3 ml vs. those who did not receive KCL (570 min vs. 890 min, $p < .006$). Lohr et al. [16] similarly found a shorter mean procedure time for D&E in those who received intracardiac KCL 15% 1–3 mL when compared to those who did not receive KCL (12.7 ± 5 min vs. 16.1 ± 7.9 min, $p < .001$).

Table 1-
Descriptive data from studies evaluating pharmacologic induction of fetal demise prior to abortion

Study	Study type	Location of the study	Gestational age range of study participant in weeks	Number of participants	Drug type and dose	Route of administration	Site of administration	Intervention group	Control group (N)
Primary outcome – Success in achieving fetal demise									
White 2016	RCT	USA	20–24	268	Digoxin 1 mg	Transabdominal	Intra-fetal or intra-amniotic	D&E following feticide with intra-fetal digoxin N= 136	D&E following feticide with intra-amniotic digoxin N= 132
Chen 2009	RCT	Taiwan	24–38	26	KCL 6 mmol and Lidocaine 10 mL of 2%	N/A	Intracardiac	Medical termination following fetal demise with KCL N= 19	Medical termination following fetal demise with lidocaine N= 7
Molaei 2008	Cohort	USA	17–24	1795	Digoxin 0.125–1 mg	Transabdominal	Intra-fetal or intra-amniotic	D&E following feticide with intra-fetal digoxin N= 1664	D&E following feticide with intra-amniotic digoxin N= 131
Primary outcome- Procedure time									
Dean 2012	Cohort	USA	18–24	1079	Digoxin 1 mg	N/A	Intra-fetal or intra-amniotic	D&E following feticide with digoxin N= 566	D&E without fetal demise N= 513
Lohr 2018	Cohort	Britain	18–24	2018	KCL 1–3 mL of 15%	N/A	intracardiac	D&E following feticide with KCL N= 288	D&E without fetal demise N= 255
Primary outcome - Safety and effectiveness									
Toce 2013	Cohort	USA	18–22	1493	Digoxin 0.5–3 mg	Trans-cervical	Intra-fetal intra-amniotic	D&E following feticide with intra-fetal digoxin N= 57	D&E following feticide with intra-amniotic digoxin N= 1436
Nucatola 2010	RCT	USA	18–24	52	Digoxin 1–1.5 mg	N/A	Intra-fetal intra-amniotic	D&E following feticide with intra-fetal digoxin N= 26	D&E following feticide with intra-amniotic digoxin N= 26
Primary outcome - Induction to expulsion interval									
Elimian 1999	Cohort	USA	18–24	68	KCL 2 mEq/mL 2–3 mL	Transabdominal	Intracardiac	Medical termination with 20 mg PGE2 vaginally every 4 hrs. Following fetal demise with KCL N= 17	Medical termination of pregnancy without fetal demise N= 51

3.4. Side effects

Three studies compared side effects during follow up among groups that did and did not receive feticidal agents [16,20,21]; these studies could not be combined due to heterogeneity. Elimian et al. [21] found no difference in side effects (nausea, vomiting, and diarrhea in combination) between the cohorts who received KCL 2 mEq/mL 2–3 mL intracardiac and those who did not prior to medical abortion using 20 mg PGE2 (47% vs. 51%, p=.78). Lohr et al. [16] similarly found no difference in severe nausea and vomiting between those who received KCL 15% of 1–3 mL intracardiac vs. no KCL prior to D&E (11.1 vs. 9.3%, p=.9).

Only White and colleagues reported side effects when comparing intra-fetal vs. intra-amniotic digoxin. White et al. [20] compared the risk of nausea, vomiting, and diarrhea among those who received digoxin 1 mg intra-fetal vs. intra-amniotic and did not find a difference between the groups; nausea (46% vs. 53%, p=.31), vomiting (27% vs. 22%, p=.53) and diarrhea (6% vs. 4%, p=.75).

3.5. Patient and provider acceptability and patient satisfaction

No study investigated provider satisfaction or acceptability. One study compared the acceptability of the surgical abortion between women who received and did not receive KCL 15% 1–3 mL intracardiac [16] and found no difference between the groups. In this study, 3.4% of

Table 2
Summary of risk of bias for the three randomized controlled trials included in the systematic review

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias) (all outcomes)	Blinding participants and personnel (performance bias)	Incomplete outcome data (attrition bias) (all outcomes)	Selective reporting (reporting bias)	Other sources of bias
Chen 2009	Low (Randomization- using computer generated random list)	High (used odd vs. even (no allocation concealment))	High (no blinding)	High (no blinding)	Low (no loss to follow up)	Low	Unclear
Nucatola 2010	Low (Randomization- using computer generated random list)	Low (used a sealed opaque envelope)	High (outcome assessors not blinded)	High (surgeons not blinded)	Low (no loss to follow up)	Low	High (sample size low to detect a difference)
White 2016	Low (Randomization scheme prepared using a random number table)	Low (used a sealed opaque envelope)	High (no blinding)	High (no blinding)	Low risk (no loss to follow up)	Low	High (sample size was low to detect a difference)

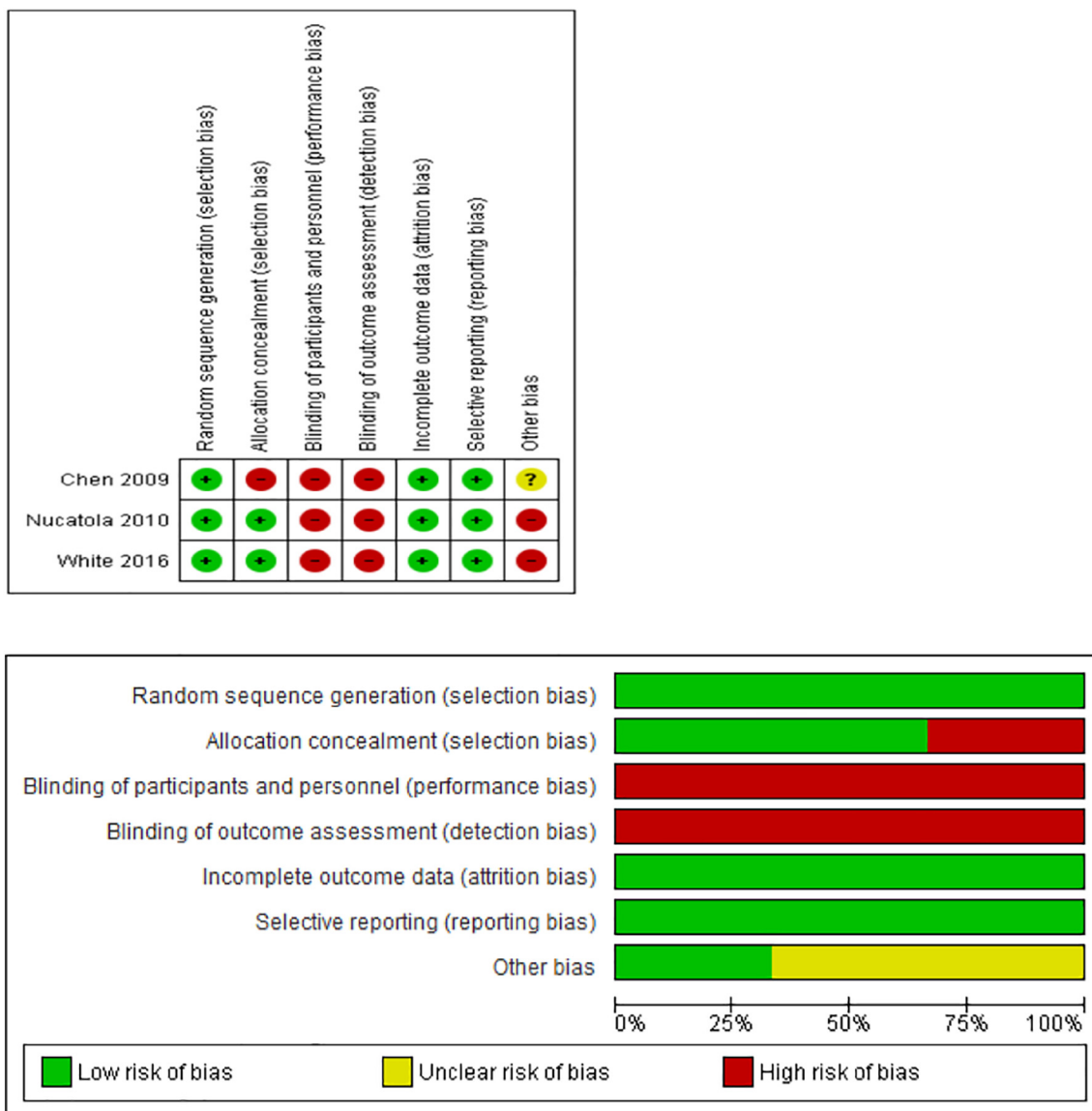


Fig. 2. (A) Summary risk of bias for three trials included in systematic review for drugs used induce fetal demise prior to abortion: low (+), high (-) or unclear (?) (B) Each risk of bias is shown as a percentage.

Table 3
Summary of risk of bias for the five observational studies included in the systematic review

	Bias due to selection of participants	Bias due to Confounding	Bias in the measurement of the intended intervention	Bias in selection of reported results	Bias due to departure from the intervention	Bias in measurement of the outcome	Bias due to missing data	Overall risk of bias judgment
Dean 2012	Moderate (no fatal flaws)	Serious (no blinding)	Low (standardized definition used to measure the outcome)	Low (outcomes mentioned at the beginning of the study)	Low (No loss to follow up)	Low (none)	Low (none)	Serious
Elimian 1999	Moderate (no fatal flaws)	Serious (no blinding)	Low (standardized definition used to measure the outcome)	Low (outcomes mentioned at the beginning of the study)	Low (no loss to follow up)	Low (none)	Low (none)	Serious
Lohr 2018	Moderate (no fatal flaws)	Serious (no blinding)	Low (standardized definition used to measure the outcome)	Low (outcomes mentioned at the beginning of the study)	Low (there is loss to follow up, but less than 10%)	Low (none)	Low (none)	Serious
Molaei 2008	Serious (fatal flaw)	Serious (no blinding)	Low (standardized definition used to measure the outcome)	Low (outcomes mentioned at the beginning of the study)	Low (no loss to follow up)	Low (none)	Low (none)	Serious
Tocce 2013	Serious (fatal flaw)	Serious (no blinding)	Low (standardized definition used to measure the outcome)	Low (outcomes mentioned at the beginning of the study)	Low (No loss to follow up)	Low (none)	Low (none)	Serious

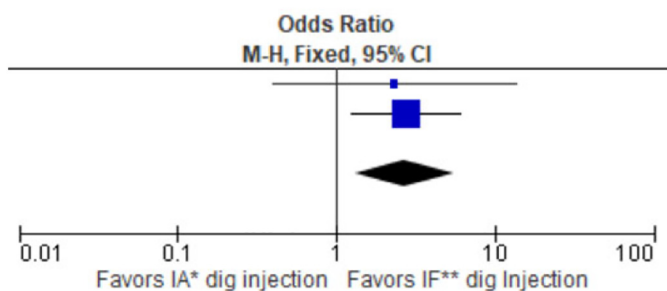


Fig. 3. Forest Plot comparing the success of intra-fetal vs. intra-amniotic administration of digoxin among the two included randomized controlled trials. *Intra-amniotic, **Intra-fetal.

patients who received KCL described the surgical abortion procedure as unacceptable as compared to 2.7% of the patients who did not receive a fetocidal agent ($p=.2$).

4. Discussion

Our systematic review identified eight studies evaluating fetocidal agents (digoxin, KCL, and lidocaine) prior to abortion. Based on the outcome from two RCTs and two observational studies, intra-fetal administration of digoxin was superior to intra-amniotic digoxin administration in achieving fetal demise at 24 h post-injection. One RCT found no significant difference in the success of achieving fetal demise between 1 and 1.5 mg of digoxin, while an observational study found a significant increase in success at a dose of ≥ 1 mg vs. < 1 mg. Intracardiac lidocaine was superior to intracardiac KCL in achieving fetal demise at 3 min post-injection [12], but this finding was from a single study with small sample size, thus should be interpreted cautiously.

Concomitant cardiac tamponade by instillation of 10–20 mL of normal saline into the pericardium increased the success rate of achieving fetal demise in both intracardiac lidocaine and intracardiac KCL administration. Inducing fetal demise with intracardiac KCL also reduced abortion time significantly for both medication abortion and D&Es. The difference in time with medication abortion was 320 min, which is both statistically and clinically significant. The 3.5 min difference in D&E time was likely of limited, if any, clinical significance.

The overall complication rate in our review was low, similar to other clinical studies [22,23]. The risk of experiencing hemorrhage requiring transfusion, cervical tear, and uterine perforation was not different between those who did or did not receive digoxin. However, pre-procedure expulsion, hospital re-admission, and presence of one or more signs of infection were higher in those who received intra-fetal or intra-amniotic digoxin, but not in those who received intracardiac KCL or lidocaine. The limited numbers of subjects receiving KCL and lidocaine and the lack of any studies comparing digoxin with either KCL or lidocaine make it difficult to reach any firm conclusion on their

comparative safety. A well-powered study evaluating all three agents would be very helpful in clarifying this issue.

Other side effects (nausea, vomiting, and diarrhea) were similar between those who received digoxin or KCL and those who did not [16,20,21]. None of these studies were powered to make strong conclusions about side effects. Despite an increase in the risk of some serious maternal adverse events, patient acceptability of the abortion procedure with or without feticide was similar [16]. Thus, beyond safety, efficacy, and efficiency, increased research efforts should be made to investigate whether the delivery of care is patient-centered, timely, and equitable [24].

4.1. Strengths and limitations

The review includes a detailed literature search without language restrictions and inclusion of studies from three continents. The review also covers a wide range of gestational ages, from 17 to 37 weeks. This review does have some limitations. There is marked heterogeneity between the eight studies, only three of which were RCTs, making comparisons somewhat difficult.

No study addressed all the outcomes of interest. In all eight studies, fetocidal agent administration and outcome assessment was ultrasound-dependent, and thus generalizability of these findings to settings with limited access to ultrasound was difficult to discern. While ultrasound guidance is standardly used in all studies evaluating fetocidal injection, none of these studies provided data concluding that ultrasound is necessary or required for intra-amniotic administration of digoxin.

In clinical settings that lack consistent ultrasound availability, intra-amniotic digoxin administration without ultrasound guidance is a viable option, and locally standard means of assessing fetal cardiac activity (fetoscope, Doppler) can be used to determine success. Only one study included lidocaine, and that arm had only seven subjects, limiting the ability to make any conclusions regarding the safety or efficacy of lidocaine for inducing fetal demise.

This review also covered a wide range of different gestational ages, making it difficult to examine the effect of gestational age on the safety and efficacy of the drugs. Several important outcomes related to serious adverse maternal outcomes and side effects are derived from only three studies. Most importantly, none of the RCTs.

reported on the adverse events of pre-procedure expulsion, hospital readmission, or the presence of one or more signs of infection. These outcomes should therefore be interpreted cautiously.

Few comparative studies have evaluated the effectiveness, potential complications, or acceptability of different fetocidal agents. Data from included cohort studies support the efficacy of intra-fetal and/or intra-amniotic digoxin, intracardiac KCL, and intracardiac lidocaine in achieving pre-abortion fetal demise. Evidence from two randomized trials, including one adequately powered study, suggests that intra-fetal rather than intra-amniotic digoxin is more effective at inducing fetal demise. Limited available evidence from observational studies suggests that fetocidal agents may reduce abortion time for medical abortion, and pos-

Table 4
Serious maternal adverse events related to using digoxin, KCL or lidocaine in inducing fetal demise prior to abortion

Adverse event	Study	Study design	Intervention vs. comparator	Rate in intervention	Rate in comparator	p
Pre-procedure expulsion	Dean 2012	cohort	D&E with digoxin vs. no digoxin	11/566 (1.94%)	0/513(0%)	<.001
	Lohr 2018	cohort	D&E with KCL vs. no KCL	3/288 (1%)	2/255 (0.78%)	.7
Hospital readmission	Dean 2012	cohort	D&E with digoxin vs. no digoxin	11/566 (1.9%)	0/513	<.001
One or more sign of infection	Dean 2012	cohort	D&E with digoxin vs. no digoxin	19/566 (3.4%)	3/513 (0.6%)	<.001
	Dean 2012	cohort	D&E with digoxin vs. no digoxin	7/566 (1.2%)	1/513 (0.2%)	.08
Temperature more than 38 °C	Elimian 1999	cohort	Medical termination with KCL vs. no KCL	9/17 (52.9%)	28/51 (54.9%)	.89
Hemorrhage requiring transfusion	Dean 2012	cohort	D&E with digoxin vs. no digoxin	3/566 (0.53%)	3/513 (0.6%)	.9
	Lohr 2018	cohort	D&E with KCL vs. no KCL	1/288 (0.25%)	0/255	.3
Uterine perforation	Dean 2012	cohort	D&E with digoxin vs. no digoxin	2/516 (0.4%)	1/513 (0.2%)	.63
Cervical laceration requiring repair	Dean 2012	cohort	D&E with digoxin vs. no digoxin	8/566 (1.4%)	6/513 (1.2%)	.72
	Lohr 2018	cohort	D&E with KCL vs. no KCL	2/288 (0.69%)	7/255 (2.7%)	.06

sibly D&E. This advantage of feticide is more pronounced in low- and middle-income countries, where medical abortion is most commonly used in the second trimester. Even in the settings where ultrasound availability is limited, intra-amniotic administration of digoxin is possible and detection of fetal cardiac activity can be performed via usual clinical practice.

There is a significant research gap in clinical trials comparing different feticidal agents, as well as those comparing feticide vs. no feticide in terms of safety and effectiveness. Thus, we recommend well designed, randomized controlled trials comparing the safety, efficacy, and acceptability of these drugs. We further recommend that more studies should be conducted in diverse settings to demonstrate the experience of using these agents with and without the use of ultrasound, as well as examining the technical expertise required for second trimester transcervical/transabdominal intracardiac administration of drugs.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conx.2020.100046>.

References

- [1] Bearak J, Popinchalk A, Ganatra B, Moller A-B, Tunçalp Ö, Beavin C, et al. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990–2019. *Lancet Glob Health*. 2020;8:e1152–61.
- [2] Drey EA, Foster DG, Jackson RA, Lee SJ, Cardenas LH, Darnay PD. Risk factors associated with presenting for abortion in the second trimester. *Obstet Gynecol*. 2006;107:128–35.
- [3] Foster DG, Kimport K. Who seeks abortions at or after 20 weeks? *Perspect Sex Reprod Health*. 2013;45:210–8.
- [4] Upadhyay UD, Weitz TA, Jones RK, Barar RE, Foster DG. Denial of abortion because of provider gestational age limits in the United States. *Am J Public Health*. 2014;104:1687–94.
- [5] Dean G, Colarossi L, Lunde B, Jacobs AR, Porsch LM, Paul ME. Safety of digoxin for fetal demise before second-trimester abortion by dilation and evacuation. *Contraception*. 2012;85:144–9.
- [6] Evans MI, Ciorica D, Britt DW, Fletcher JC. Update on selective reduction. *Prenat Diagn Publ Affil Int Soc Prenat Diagn*. 2005;25:807–13.
- [7] J D, E D, undefined. Induction of fetal demise before abortion. *Contraception* 2010; 81:462–73.
- [8] Garipey AM, Chen BA, Hohmann HL, Achilles SL, Russo JA, Creinin MD. Transvaginal administration of intraamniotic digoxin prior to dilation and evacuation. *Contraception*. 2013;87:76–80.
- [9] Sharvit M, Klein Z, Silber M, Pomeranz M, Agizim R, Schonman R, et al. Intra-amniotic digoxin for feticide between 21 and 30 weeks of gestation: a prospective study. *BJOG*. 2019;126:885–9.
- [10] Sfakianaki AK, Davis KJ, Copel JA, Stanwood NL, Lipkind HS. Potassium chloride-induced fetal demise. *J Ultrasound Med*. 2014;33:337–41.
- [11] Denny CC, Baron MB, Lederle L, Drey EA, Kerns JL. Induction of fetal demise before pregnancy termination: practices of family planning providers. *Contraception*. 2015;92:241–5.
- [12] Chen C-H, Chen T-H, Kuo S-J, Chen C-D, Yang Y-S, Chen M. Late termination of pregnancy: experience from an east Asian population and report of a novel technique for feticide. *J Med Ultrasound*. 2009;17:193–9.
- [13] Govender L, Moodley J. Late termination of pregnancy by intracardiac potassium chloride injection: 5 years' experience at a tertiary referral Centre. *S Afr Med J*. 2013;103:47–51.
- [14] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015 Jan 1; 4:1.
- [15] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- [16] Lohr PA, Parsons JH, Taylor J, Morroni C. Outcomes of dilation and evacuation with and without feticide by intra-cardiac potassium chloride injection: a service evaluation. *Contraception*. 2018;98:100–5.
- [17] Molaei M, Jones HE, Weiselberg T, McManama M, Bassell J, Westhoff CL. Effectiveness and safety of digoxin to induce fetal demise prior to second-trimester abortion. *Contraception*. 2008;77:223–5.
- [18] Nucatola D, Roth N, Gatter M. A randomized pilot study on the effectiveness and side-effect profiles of two doses of digoxin as fetocide when administered intraamniotically or intrafetally prior to second-trimester surgical abortion. *Contraception*. 2010;81:67–74.
- [19] Tocce K, Sheeder JL, Edwards LJ, Teal SB. Feasibility, effectiveness and safety of transvaginal digoxin administration prior to dilation and evacuation. *Contraception*. 2013;88:706–11.
- [20] White KO, Nucatola DL, Westhoff C. Intra-fetal compared with intra-amniotic digoxin before dilation and evacuation: a randomized controlled trial. *Obstet Gynecol*. 2016;128:1071–6.
- [21] Elimian A, Verma U, Tejani N. Effect of causing fetal cardiac asystole on second-trimester abortion. *Obstet Gynecol*. 1999;94:139–41.
- [22] Singh S, Seligman NS, Jackson B, Berghella V. Fetal Intracardiac potassium chloride injection to expedite second-trimester dilation and evacuation. *Fetal Diagn Ther*. 2012;31:63–8.
- [23] Steward R, Melamed A, Kim R, Nucatola D, Gatter M. Infection and extramural delivery with use of digoxin as a feticidal agent. *Contraception*. 2012;85:150–4.
- [24] WHO | What is Quality of Care and why is it important? https://www.who.int/maternal_child_adolescent/topics/quality-of-care/definition/en/ (accessed September 23, 2020).