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Intra-amniotic digoxin for feticide between 21 and 30 weeks of gestation: a prospective study

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Objective Intra-amniotic injection of digoxin is a well-known method for feticide before inducing a termination of pregnancy (TOP) at 17–24 weeks of gestation. Information on its effectiveness when administered after 24 weeks of gestation is limited. This study evaluated the efficacy of intra-amniotic digoxin injection for inducing fetal demise within 18–24 hours, at 21–30 weeks of gestation, and its safety.

Design Prospective cohort study.

Setting Tertiary university medical centre.

Population Women at 21–30 weeks of gestation with a singleton pregnancy, admitted for TOP.

Methods Intra-amniotic injection of 2 mg of digoxin was performed 1 day before medical TOP. Fetal heart activity was evaluated by ultrasound for 18–24 hours after the injection. Serum digoxin level and maternal electrocardiogram (ECG) were evaluated 6, 10, and 20 hours after injection.

Main outcome measure Frequency of successful fetal demise.

Results Fifty-nine women participated in the study. The mean gestational age was 24^{+2} weeks (range 21^{+0}–30^{+0}), with 29 (49.2%) beyond 24^{+0} weeks of gestation. Fetal cardiac activity arrest was achieved in 55/59 cases (93.2%). Normal maternal ECG recordings were noted in all cases. Mean serum digoxin levels 6 and 10 hours after injection were in the therapeutic range (1.3 ± 0.7 ng/l and 1.24 ± 0.49 ng/l, respectively) and below the toxic level (2 ng/l). Extramural delivery following digoxin did not occur. There were no cases of chorioamnionitis.

Conclusion Intra-amniotic digoxin for feticide at 21–30 weeks of gestation in a singleton pregnancy appears effective and safe before TOP at advanced gestational ages.

Keywords Digoxin, fetal demise, medical termination of pregnancy, second trimester, termination of pregnancy.

Tweetable abstract This study shows that feticide by intra-amniotic digoxin injection at 21–30 weeks of gestation appears effective and safe.

Linked article This article is commented on by FA Chervenak and LB McCullough, p. 890 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15626.

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Introduction

The field of perinatal genetics and fetal diagnostic techniques have made extensive technological strides in the ability to diagnose fetal anomalies that might lead families to consider pregnancy termination; however, many anomalies cannot be diagnosed until later in pregnancy. Life-threatening maternal events might also necessitate the termination of pregnancy (TOP). The World Health Organization (WHO) recommends pre-procedural feticide after 20 weeks of gestation to avoid the delivery of a viable fetus following a TOP.

Cardiocentesis with potassium chloride injection is one of the most common methods of feticide,[1–3] and is considered safe.[1] The procedure is challenging for the physician and the patient, however, because it usually requires a skilled specialist, can be painful, and frequently leads to additional emotional stress for the patient and their partner.[4]

Since the 1980s, digoxin injection into the amniotic fluid has often been used to induce fetal demise before dilatation

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and evacuation or medical TOP at 17–24 weeks of gestation. Despite the wide use of digoxin for feticide, there is no consensus about the optimal dose or route of administration. Although feticide with digoxin is considered effective, with no major complications reported,[5–10] information regarding its usefulness and safety after 24 weeks of gestation is limited.

In Israel, it is legal to perform TOP after 24^{+0} weeks of gestation if severe or incurable fetal anomaly or malformation is diagnosed, or for exceptional psychosocial reasons. After approval from a special committee, feticide can be performed to avoid the delivery of a live fetus in these complicated cases.

We conducted this prospective study to evaluate the success and safety of feticide with intra-amniotic digoxin injection up to 30 weeks of gestation. In this experimental intervention, we hypothesised that fetal demise could be successfully achieved with minimal complications.

Methods

All eligible women at 21–30 weeks of gestation admitted to the gynaecology ward at Meir Medical Center for TOP from 1 May 2011 through to 28 February 2016 were offered enrolment in the study. Departmental policy is to perform feticide before TOP after 22^{+0} weeks of gestation or before 22 weeks of gestation if the ultrasound-estimated fetal weight is more than 500 g.

The primary outcome of the study was to evaluate the efficacy of a 2-mg intra-amniotic digoxin injection to induce feticide (defined as absent fetal cardiac activity) within 18–24 hours, at 21–30 weeks of gestation. The secondary outcome was to evaluate the safety of this method. There was no patient or public involvement in this study, and no specific funding was required for this study.

Inclusion criteria were healthy women with a singleton pregnancy, admitted for TOP, who needed the induction of fetal demise before medical TOP. Exclusion criteria were a gestational age of less than 21 weeks or more than 30 weeks. Additional exclusion criteria were women with past or active cardiac disease, chronic renal disease, chronic liver disease, electrocardiogram (ECG) changes on admission, high blood pressure on admission, coagulation dyscrasia on admission, preterm premature rupture of membranes, and potential technical difficulties at injection, such as severe oligohydramnios or uterine anomalies.

Each participant provided signed informed consent. ECG and blood tests (complete blood count for baseline haemoglobin, leucocyte, and platelets, and chemistry, including creatinine and liver enzyme) were performed to verify eligibility. Under ultrasound guidance, 2 mg of digoxin was injected transabdominally into the amniotic fluid 1 day before the planned medical TOP. Vital signs, serum digoxin level, and ECG were evaluated at 6, 10, and 20 hours following injection. Fetal cardiac activity was assessed via ultrasonography at 18–24 hours after injection. After fetal demise, medical TOP was induced. The medical method used for termination of pregnancy was left to the discretion of the physician. If fetal demise was not achieved by intra-amniotic digoxin injection, intracardiac potassium chloride was injected. Post-delivery, the absence of signs of life was confirmed.

A dose of 2 mg of digoxin was chosen because of the advanced gestational age, even though lower doses have been described to be satisfactory for feticide at 17–24 weeks of gestation.[10,11] Intra-amniotic injection was chosen because it is easier to perform and does not require specialised skills.[12]

Women who did not meet the inclusion criteria or declined to enrol underwent feticide with potassium chloride cardiocentesis followed by medical TOP.

Statistical analysis was performed using SPSS® 20.0 for WINDOWS (SPSS Inc., Chicago, IL, USA). Descriptive statistics were analysed by mean and standard deviation for quantitative parameters and by percentage for qualitative parameters.

Results

During the study period, 63 patients were enrolled to receive intra-amniotic digoxin. Two patients were excluded after ultrasound evaluation revealed oligohydramnios and two patients were excluded for twin pregnancy. Fifty-nine women with singleton pregnancies were included in this study.

The clinical characteristics of the study group are shown in Table 1. Indications for TOP included major morphological abnormalities in 28 patients (47.5%), genetic defects in 16 patients (27%), cytomegalovirus infection in three patients (5%), and obstetric indications, such as inevitable miscarriage near the limits of viability in four patients (7%) and complicated psychosocial reasons in eight patients (13.5%).

Table 1. Clinical characteristics of the study group (n = 59)

Maternal age (years ± SD)	30.4 ± 6.3
Gestational age (weeks ± SD)	24.2 ± 2.9
Gravidity (±SD)	2.5 ± 1.7
Primigravida *n* (%)	19 (32)
Multigravida *n* (%)	40 (68)
Nulliparous *n* (%)	21 (35.6)
Multiparous *n* (%)	38 (64.4)
BMI (kg/m^2) (n = 43) (mean ± SD)	26.4 ± 6.5
Indication for termination of pregnancy *n* (%)	
Genetic chromosomal disorder	16 (27)
Morphological defect	28 (47.5)
Obstetric	4 (7)
Psychosocial	8 (13.5)
Cytomegalovirus infection	3 (5)

The mean maternal age was 30.4 years (range 17–45) and the mean gestational age was 24^{+2} weeks (range 21^{+0}–30^{+0} weeks). The gestational age was beyond 24^{+0} weeks in 29 patients (49.2%). Almost all participants underwent a medical TOP, primarily with the administration of extra-amniotic prostaglandin E2 in 22 patients (37.2%) or misoprostol prostaglandin E1 in 18 patients (30.5%). Other methods included intravaginal prostaglandin E2 in seven patients (12%), combined methods in six patients (10.2%), oxytocin injection BP (Rotexmedica, Trittau, Germany) in one patient (1.7%), and double-balloon catheter in one patient (1.7%). Three women (5%) experienced spontaneous labour and delivery after feticide during hospitalisation with no extramural delivery, and one woman (1.7%) underwent a hysterotomy as a result of two previous caesarean sections and placenta praevia.

The primary study outcome of feticide was successful in 55 cases (93.2%). Four patients required potassium chloride cardiocentesis after digoxin injection, as summarised in Table 2: one because of a rupture of membranes 1 hour after the digoxin injection and three because of sustained fetal heart activity 18–24 hours after injection. Of these, two women were in obesity classes II and III, as defined by the WHO classification (with a body mass index, BMI, of 39.9 and 41.8 kg/m^2, respectovely), and one woman was at 27 weeks of gestation with a normal BMI.

All participants had normal vital signs and normal ECG tracings during the procedure. The mean maternal serum digoxin level 6 hours after injection was 1.3 ± 0.7 ng/l (range 0.16–3.2 ng/l). After 10 hours, it was 1.24 ± 0.49 ng/l (range 0.4–2.5 ng/l), and after 20 hours, it was 1.17 ± 0.47 ng/l (range 0.3–1.9 ng/l). There were no cases of chorioamnionitis based on clinical evaluation (uterine tenderness, or purulent or foul odour of the amniotic fluid), but not by amniocentesis. Fifteen women (25%) had fever (>38°C) during or following the medical TOP, without any other signs of chorioamnionitis. Most of these women with fever complications (86%) had an induction with prostaglandins. None of the patients had complications related to feticide, as defined in the secondary outcome (no digoxin toxicity and no chorioamnionitis).

One woman experienced coronary spasm during placental removal, 3 days after digoxin injection. The method used for the TOP was vaginal prostaglandin E1 at 27 weeks of gestation. After expulsion of the fetus, the placenta needed surgical removal. During the placental removal, the patient experienced severe postpartum haemorrhage, chest pain, high blood pressure, and ECG changes. The differential diagnosis included amniotic fluid emboli, pulmonary embolism, or cardiac event as a result of hypovolemic shock. Computed tomography (CT) angiography ruled out an embolic event and cardiac spasm was the working diagnosis, as she improved spontaneously.

Discussion

Main findings

This study evaluated the usefulness and safety of feticide with intra-amniotic digoxin injection just prior to TOP, performed up to 30 weeks of gestation. The primary study outcome was the efficacy of intra-amniotic digoxin injection as a method of feticide at 21–30 weeks of gestation. The secondary outcome was to evaluate the safety of this method. Previous studies described the effectiveness of this feticide method up to 24 weeks of gestation only.[5,6,9,10] We report our experience with 59 cases of feticide performed at advanced gestational ages with a high success rate (93.2% experienced fetal demise after 18–24 hours) and adequate safety (no digoxin toxicity and no chorioamnionitis).

Strengths and limitations

This study was limited by its descriptive nature and the lack of a control group to compare adverse events. Another limitation of the study was heterogeneity of the abortive agent and that the fetal extraction was performed by several physicians, which could affect the complication rate. The study lacks a participant experience questionnaire.

The strengths of this study are that it describes the first cohort of feticide performed with digoxin at 20–30 weeks of gestation. All patients were treated in a single medical centre with a standardised medical approach and treatment protocols.

Interpretation

Jackson et al. reported a randomised trial of 126 women, half of whom received intra-amniotic 1 mg digoxin and

Table 2. Digoxin failures

Case	Maternal age	Gestational age	Gravity	Parity	BMI	Indication for termination of pregnancy
1	29 years	24.2 weeks	3	2	39.9 kg/m^2	Trisomy 21
2	35 years	23.4 weeks	1	0	41.8 kg/m^2	Deletion in comparative genomic hybridisation
3	29 years	27.1 weeks	2	1	20.0 kg/m^2	DiGeorge syndrome
4	38 years	23.1 weeks	5	3	23.2 kg/m^2	Inevitable miscarriage

half of whom received saline as a placebo.[9] Five women (8%) had persistent fetal cardiac activity on the following day. Others reported almost 100% success for intra-amniotic digoxin doses of at least 1 mg.[5,11,13] Our 6.7% failure rate (four cases) correlates with the rates of 0–8% published in the literature. Our first failure was in a patient who experienced the rupture of membranes 1 hour after amniocentesis for the digoxin injection. The indications for TOP were vaginal bleeding, placental haematoma, and threatened miscarriage near the limits of viability. This case should have been considered for feticide by potassium chloride injection, which provides immediate asystole, instead of digoxin. Two other failures may be attributable to morbid obesity. These two women had the highest BMIs (39.9 and 41.8 kg/m^2) in the cohort, and we did not find any other cause that might explain these failures. It is possible that maternal obesity may affect intrauterine processes, but this requires additional study.

To assess the safety of the procedure, we evaluated serum digoxin levels 6, 10, and 20 hours after the digoxin injection. Mean values were in the therapeutic range and below the toxic level (2 ng/l). This is similar to the results reported by Drey et al.[5] Serum digoxin levels were normal, although we encountered one major complication. A case of coronary spasm occurred during placental evacuation, 3 days after the digoxin injection, and was attributed to hypovolemic shock.

Some authors proposed that digoxin injection can stimulate spontaneous miscarriage at a rate of 0.12–1.90%.[11,14,15] The wide range is attributed to intra-amniotic versus intrafetal and transabdominal versus transvaginal injection modalities. Dean et al.[14] suggested that intra-amniotic injection might carry a higher risk for spontaneous miscarriage as compared with intrafetal injection. Our results of 5% spontaneous miscarriage were higher than reported in the literature, higher than the risk for pregnancy loss after second-trimester amniocentesis (0.6–1.0%),[16,17] and higher than the risk for preterm delivery after third-trimester amniocentesis (1.2–3.0%).[18,19] The differences could be linked to patient factors, as two of the three had TOP for obstetric causes of cervical dynamics and mid-trimester bleeding. Those two patients were admitted with threatened mid-trimester miscarriage near the limits of viability. The spontaneous labour might have started before the digoxin injection. Digoxin might induce prostaglandin release that can stimulate cervical ripening,[12] as one study reported inflammatory responses 24 hours after intra-amniotic digoxin injection for TOP at 19–23 weeks of gestation.[20] We considered that these factors contributed to the spontaneous fetal expulsion after digoxin injection.

In our cohort, 15 (25%) women experienced fever, without other evidence of chorioamnionitis (uterine tenderness, or purulent or foul odour of the amniotic fluid); 13 had induction with prostaglandins, misoprostol, or extra-amniotic prostaglandin E2 (PGE2). Fever rates were 31.8% in the misoprostol group and 28.5% in the extra-amniotic PGE2 group. In accordance with previously reported results, fever is a common side effect of misoprostol and PGE2, reported at frequencies of 10–30% in late second-trimester TOP with misoprostol.[21–24] In a prospective randomised trial comparing the efficacy and safety of misoprostol with PGE2 in a cohort of 55 women at 12–22 weeks of gestation undergoing TOP, 63% of the PGE2 group and 11% of the misoprostol group experienced fever.[25]

Conclusion

The study showed that a 2-mg intra-amniotic digoxin injection is an effective method of feticide between 21 and 30 weeks of gestation, and appears to be safe. Further evaluation of the procedure, with a larger series, is warranted to better identify the optimal digoxin dose and outline the potential efficacy and side effects of this method.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MS performed data management, analysis, and drafted the manuscript. ZK, MP, and RA planned and implemented the protocol of the study. MS helped with data analysis. RS implemented the protocol, and helped with the analysis and drafting of the manuscript. AF planned the study and oversaw the analysis and drafting of the manuscript.

Details of ethics approval

This prospective cohort study was approved by the Meir Medical Centre Institutional Ethics Committee on 23 August 2012 (approval no. 0077-12-MMC). It was registered at www.ClinicalTrials.gov (NCT01951079).

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