ORIGINAL ARTICLE

# Effectiveness of 1mg and 2mg Intra Amniotic Digoxin for Fetal Demise in Second-trimester Anomaly: A Cross Sectional Study

**Rajesh Adhikari[1], Padma Raj Dhungana[1], Prem Raj Pageni[1], Shyam Sundar Parajuly[2], Kalpana Gautam Adhikari[3]**

[1] Associate Professor, Department of Obstetrics and Gynecology, Pokhara Academy of Health Sciences, Western Regional Hospital, Ramghat 10, Kaski, Pokhara, Nepal.
[2] Medical Sonography officer, Pokhara Academy of Health Sciences, Western Regional Hospital, Ramghat 10, Kaski, Pokhara, Nepal.
[3] Lecturer, Department of Microbiology, Janapriya Multiple Campus, Pokhara, Nepal.

## Article History

Received: 3rd December, 2023
Acceptance: 14th January, 2024

Online Access

DOI:

## Corresponding Author:

**Rajesh Adhikari**
Associate Professor,
Department of Obstetrics and Gynecology, Pokhara Academy of Health Sciences, Western regional Hospital, Pokhara Nepal.
Email: adhikarirajesh007@hotmail.com

## Abstract

**Introduction:** Inducing fetal demise before termination after near viable gestational ages is practiced widely to avoid signs of life at delivery and reduce emotional trauma to the mother and her family. Digoxin is instilled by intra-fetal or intra-amniotic routes at varying doses. In this study, we have used intra-amniotic digoxin and simultaneously compared the effectiveness of two doses of digoxin 1 mg and 2 mg.

**Methods:** This was a hospital-based Cross Sectional study conducted in the Department of Obstetrics and Gynecology at Pokhara Academy of Health Sciences from 1/1/2021 to 30/6/2021. A total of 24 pregnant women with gestational age sranging from 20 to 28 weeks with fetal anomalies confirmed by ultrasonography were enrolled in the study This time interval is the optimum time to detect fetal anomaly in second trimester. Ultrasound-guided intra-amniotic digoxin as 1 mg and 2 mg were instilled serially. Fetal cardiac activity was checked by ultrasound at 18 hours and 24 hours of digoxin injection.

**Results:** Among 24 cases of fetal anomaly, the majority occurred in primigravida (n = 14, 58.3%) with a mean age of 24.6 years and mean gestational age of 24.4 weeks. The most common fetal anomaly was hydrocephalus (n = 9, 37.5%) followed by anencephaly (n = 6, 25%). Among 24 cases only one case had persistent fetal cardiac activity after 24 hours of digoxin who was at 28 weeks of gestation and had received 1 mg of digoxin.

**Conclusion:** Intra-amniotic injection of digoxin 1 mg is as effective as 2 mg at causing fetal demise by 18-24 hours.

***Keywords:*** Fetal anomaly, fetal demise, intra-amniotic digoxin

## Introduction

The incidence of fetal anomaly in the general population is 2-3%.[1] Congenital anomalies account for 20-25% of perinatal deaths.[1] Advanced diagnostic techniques have made it easier to diagnose fetal anomalies that could provide parents with a choice to consider pregnancy termination.[2]

Abnormal fetuses cause psychological and emotional trauma to the mother and her family and even the cost of care is greater because of attendant morbidities of late diagnosis. Dealing with such cases is an ethical dilemma both for the care providers and the parents if signs of life are present at the time of birth. Induced fetal demise before medical abortion is an option to avoid such dilemma and emotional consequences in case of fetal anomaly.[3]

Induced fetal demise is the procedure of inducing fetal death before the expulsion of the fetus.Evidence has shown that the majority of women prefer the concept of fetal death before the termination of pregnancy in the anomalous fetus.[4] Furthermore, fetal demise leads to easier and faster medical abortion.[5] World Health Organization (WHO) recommends fetal demise after 20 weeks of gestation to avoid delivery of a viable fetus following termination of pregnancy whereas the Royal College of Obstetricians and Gynaecologists (RCOG)

**How to Cite this Article in Vancouver Style:**
Adhikari R, Dhungana PR, Pageni PR, Parajuly SS, Gautam KA. Effectivenessof 1mg and 2mg Intra amniotic digoxinfor fetal demise in second-trimester anomaly: A cross sectional study. Med. J. Pokhara A. Health Sci. 2024;7(1):24-27.

recommends inducing fetal demise at greater than 21 weeks 6 days of gestation[6]

Intracardiac potassium chloride is one of the most common methods of feticide, especially in developed countries which requires a skilled specialist.[7] Evidences have also shown that intra-fetal administration of digoxin is superior to intra-amniotic digoxin administration.[8] However, in resource poor countries like Nepal, intra-amniotic digoxin is widely used to induce fetal demise before second-trimester abortion because its use is comparatively simple and technically easier.[5] Though there is wide use of digoxin for feticide, data about the optimal dose and route of administration are limited. Thus, the purpose of this study was to compare the effectiveness of intra-amniotic digoxin of different dosages (1 mg and 2 mg) for fetal demise before termination of pregnancy.

## Methods

This was a hospital based cross-sectional study conducted in the Department of Obstetrics and Gynecology at Pokhara Academy of Health Sciences for six months from 1/1/2021 to 30/6/2021.Ethical approval was obtained from the Institutional Review Committee (IRC), Pokhara Academy of Health Sciences. All anomalies detected by ultrasound during the period of 20 to 28 weeks which might have fatal birth outcomes were recruited for the study. Patients visiting the Gynecology and Obstetrics outpatient department (OPD) for regular antenatal check-ups or any referral case from another institute for further evaluation were the sampling population for the study.

Severe anomalous fetuses incompatible to life and consent given by parents were included in the study. Exclusion criteria included multiplepregnancies, pre-labor rupture of membrane, and medical disorders where digoxin could not be used, like maternal hypersensitivity, maternal preexisting cardiac conditions, renal impairment and preexisting maternal electrolyte imbalance.

Participants were stratified alternately into the two arms, starting with the 1 mg digoxin injection for the first inclusion, followed by the 2 mg digoxin injection for the second inclusion, and so forth. This alternating stratification pattern continued throughout the study period, ensuring a balance in the distribution of participants between the 1 mg and 2 mg arms. The alternation was intended to minimize potential bias and account for any sequential variations in patient characteristics (gestational age, maternal health, psychological and emotional well-being, previous pregnancy, uterine scar tissue, infection status, availability of resources) over time.

Patient particulars including age, parity, and gestational age were entered in proforma. Counseling for feticide was done and informed written consent was obtained from each participant. Two different doses of digoxin 1 mg and 2 mg were injected intra-amniotically serially by a 22gauze spinal needle under Ultra Sonography (USG) guidance. Fetal cardiac activity was recorded at 18 hours by USG and if the fetal heart rate (FHR) is present then again USG is done at 24 hours of digoxin injection. If the fetal heart rate is still after 24 hours of digoxin then again 2mg of digoxin was given intra-amniotically and the fetal heart rate was seen after 18 hours. During that period mother was closely observed for any drug-related complications. Induction of labor was done with the help of misoprostol according to FIGO guideline 2017 AD.

**Data Analysis:** Patients characteristics like age, parity, gestational age, type of anomaly, and 1 or 2 mg of digoxin were entered in Microsoft Excel2020. The fetaloutcome for asystole and time taken for feticide were recorded and compared. For this ultrasound scan was performed to detect absent fetal cardiac activity.

## Results

During the study period, 24 patients were enrolled to receive intra-amniotic digoxin. The mean age was 24.6 years (range 18-35 years) and the mean gestational age was 24.4 weeks (range 21-28 weeks).

**Table 1:** Demographic characteristics of the patients (n=24)

| Demographic Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Age | | |
| <20 | 2 | 8.3 |
| 20-24 | 12 | 50.0 |
| 25-29 | 8 | 33.3 |
| 30-35 | 2 | 8.4 |
| Total | 24 | 100.0 |
| Parity | | |
| Primi | 14 | 58.3 |
| P1 | 8 | 33.3 |
| P2 | 1 | 4.2 |
| P3 | 1 | 4.2 |
| Total | 24 | 100.0 |
| Gestational Age ( Weeks) | | |
| 20-24 | 13 | 54.2 |
| 24-28 | 11 | 45.8 |
| Total | 24 | 100.0 |

Nearly half of the patients were in the age group of 20 – 24 years (50%) followed by 25 – 29 years( 33.3%). Among them, 58.3% were primigravida and were at 20- 24 weeks of gestation (54.2%)

**Table 2:** Types of anomaly of fetus (n=24)

| Anomaly | Frequency | Percentage |
|---|---|---|
| Hydrocephalus | 9 | 37.5 |
| Anencephaly | 6 | 25.0 |
| Multiple congenital anomalies | 3 | 12.5 |
| Polycystic Kidney Disease | 2 | 8.3 |
| Cystic Hygroma | 2 | 8.3 |
| Spinal defect | 2 | 8.3 |
| Total | 24 | 100.0 |

The most common fetal anomaly was hydrocephalus (37.5%) followed by anencephaly (25%), multiple congenital anomalies

(12.5%), spinal defect (8.3%), cystic hygroma (8.3%), polycystic kidney disease (8.3%).

**Table 3:** Fetal heart rate after 18 and 24 hours (n=24) and its comparison among the dosages

| FHS | Digoxin | Frequency | Percentage (%) |
|---|---|---|---|
| Absent within 18 hours | 1 mg | 11 | 45.8 |
| | 2 mg | 12 | 50 |
| Persistent after 24 hours | 1 mg | 1 | 4.2 |
| | 2 mg | 0 | 0.0 |
| Total | | 24 | 100.0 |

Among 24 cases, only 1 case had FHS present after 24 hours of digoxin. That patient was at 28 weeks of gestation and received 1 mg of digoxin. In that patient again 2 mg digoxin was given and FHS was absent within 18 hours.

The effectiveness of two different doses of digoxin (1 mg and 2 mg) was compared by assessing FHS after administration of intra-amniotic digoxin and the which suggested that there was no significant difference between the efficacy of these two different doses in causing fetal demise

There was no complication due to digoxin in any of the patients in either of the groups.

## Discussion

In this study, the mean maternal age was 24.6 years which was similar to the studies conducted by Shakya et al.(25 years) and Tufa et al. (23.4 years).[3,9] The mean gestational age in the current study was 24.4 weeks ranging from 21 to 28 weeks. In a study conducted by Sharvit et al., the gestational age ranged from 21 to 30 weeks with a mean of 24.2 weeks.[2] According to the study of Tufa et al. the mean gestational age was 23.1 weeks with a range of 20 to 27 weeks.[9] Shakya et al. study showed the mean gestational age to be 26.5 weeks ranging from 20-34 weeks.[3] The findings of all these studies were similar to this study regarding gestational age because this is usually the time when anomaly scans are mostly done and any abnormality if present is identified by ultrasonography.

The most common fetal anomaly in this study was hydrocephalus (37.5%) followed by anencephaly (25%), multiple congenital anomalies (12.5%), spinal defect (8.3%), cystic hygroma (2%), polycystic kidney disease (2%). In the study conducted by Shakya et al.,the most common anomaly was anencephaly (50%) followed by multiple fetal anomalies(18.75%).

In this study, following 2 mg intra-amniotic digoxin, cardiac activity was absent in 100% of cases within 18 hours. Eleven out of 12 cases with 1 mg digoxin had absent FHS within 18 hours. Only 1 case had persistent FHS after 24 hours of digoxin and further received an additional 2 mg of digoxin and FHS was absent within 18 hours. In the study done by Shakya et al. cardiac activity was absent in 100% of cases following 24 hours of 1mg intra-amniotic digoxin.[3] Results were comparable to the study done by Borgatta et al. in 22 women over 18 weeks of gestational age which concluded that intra-amniotic injection of digoxin 1.5 mg was effective at causing fetal demise by 20 to 24 hours.[5] In a study by Nucatola D et al, 52 women at 18-24 weeks' gestation were randomized to one of four digoxin treatment groups: doses of 1 and 1.5 mg instilled via both routes intra-amniotically or intrafetally.[10] The failure rate did not vary by route of administration and was not lowered by increasing the dose from 1-1.5mg. Thus, they concluded that both the routes are safe and effective and doses of more than 1 mg maynot be necessary for inducing fetal death before second-trimester surgical abortion.[10]

The overall failure rate of digoxin in this study was 4.2% with 1 mg of digoxinIn the study by Jackson et al. 126 women were randomized to receive either 1 mg intra-amniotic digoxin (n=62) or placebo (n=64). At 24 hours, there was a failure rate of 8%.[4]A retrospective cohort analysis of 1795 pregnant women between 17 and 24 weeks' gestation by Molaei et al. assessed varying doses of digoxin and reported no failure to induce demise at a 1 mg intra-fetal dose.[11] In a study by Borgatta et al. in 21 women, fetal cardiac activity was absent in all cases assessed at least 20 hours after intra-amniotic injection of 1.5 mg digoxin and none had any sign of toxicity.[5]

In the present study, adverse effect or complication of digoxin was not observed in any case. Similar was the finding in the study done by Drey et al. in pregnant women between 19 and 23 weeks gestation where 1 mg digoxin was administrated through intra-amniotic injection.[12] Based on limited systemic absorption and the absence of clinically significant cardiac or clotting effects, they concluded intra-amniotically administered digoxin to be safe for use before late second-trimester pregnancy terminations. White et al. compared the effectiveness of 1.0 mg intra-fetal or intra-amniotic digoxin to achieve fetal asystole before second-trimester surgical pregnancy termination.[13]

## Conclusion

Intra-amniotic digoxin can be considered safe and effective in inducing fetal demise in case of fetal anomaly in the second trimester. There is no difference in the efficacy of 1 mg and 2 mg digoxin in causing fetal demise. However, studies on larger scales are required to generalize the findings.

## References

1. Gliozheni O, Sylejmani S, Kati K. Ultrasound and Diagnosis of Fetal Anomalies. Donald School J Ultrasound ObstetGynecol. 2011 Sep 1;5(3):193-204. DOI: 10.5005/jp-journals-10009-1196

2. 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. Br J ObstetGynaecol. 2019 Jun;126(7):885-9. DOI: 10.1111/1471-0528.15640 PMID:30703286

3. Shakya B, Chaudhary P, Tumbahangphe M, Jha M. Intra-amniotic Digoxin for Fetal Anomaly in Second and Early Third Trimester. Nepal JObstetGynaecol. 2014 Sep 28;9(1):48-51. DOI: 10.3126/njog.v9i1.11188

4. Jackson RA, Teplin VL, Drey EA, Thomas LJ, Darney PD. Digoxin to facilitate late second-trimester abortion: a randomized, masked, placebo-controlled trial. Obstet Gynecol. 2001 Mar;97(3):471-6.
DOI: 10.1097/00006250-200103000-00029
PMID: 11239659

5. Borgatta L, Betstadt SJ, Reed A, Feng K tzu. Relationship of intraamniotic digoxin to fetal demise. Contraception. 2010 Apr;81(4):328-30.
DOI: 10.1016/j.contraception.2009.12.001
PMID: 20227550

6. Aynaoglu Yildiz G, Al RA. The Effect of Different Doses of Intraamniotic Digoxin on the Timing of Fetal Demise in Second Trimester Medical Abortions. Gynecol Obstet Reprod Med. 2022 Jun 16;1-4.
DOI: 10.21613/GORM.2022.1304

7. Pasquini L, Pontello V, Kumar S. Intracardiac injection of potassium chloride as method for feticide: experience from a single UK tertiary centre. Br JObstetGynaecol 2008 Mar;115(4):528-31.
DOI: 10.1111/j.1471-0528.2007.01639.x
PMID: 18271890

8. Tufa TH, Prager S, Lavelanet AF, Kim C. Drugs used to induce fetal demise prior to abortion: a systematic review. Contraception:X. 2020;2:100046.
DOI: 10.1016/j.conx.2020.100046
PMID: 33294839 PMCID: PMC7689273

9. Tufa TH, Lavelanet AF, Belay L, Seboka B, Bell J. Feasibility of intra-amniotic digoxin administration by obstetrics and gynecology trainees to induce fetal demise prior to medical abortion beyond 20 weeks. BMJ Sex Reprod Health. 2020 Oct;46(4):308-12.
DOI: 10.1136/bmjsrh-2019-200396
PMID: 32241827 PMCID: PMC7569366

10. 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 Jan;81(1):67-74.
DOI: 10.1016/j.contraception.2009.08.014
PMID: 20004276

11. 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 Mar;77(3):223-5.
DOI: 10.1016/j.contraception.2007.10.011
PMID: 18279695

12. Drey EA, Thomas LJ, Benowitz NL, Goldschlager N, Darney PD. Safety of intra-amniotic digoxin administration before late second-trimester abortion by dilation and evacuation. Am J Obstet Gynecol. 2000 May;182(5):1063-6.
DOI: 10.1067/mob.2000.105438
PMID: 10819828

13. White KO, Nucatola DL, Westhoff C. Intra-fetal Compared With Intra-amniotic Digoxin Before Dilation and Evacuation: A Randomized Controlled Trial. ACOG. Obstet Gynecol. 2016 Nov;128(5):1071-6.
DOI: 10.1097/AOG.0000000000001671
PMID: 27741192