# A Retrospective Analysis of Intra-Uterine Fetal Demise Cases in Our Clinic

# Kliniğimizde Gerçekleşen İntra-Uterin Fetal Ölüm Vakalarının Retrospektif Olarak Değerlendirilmesi

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**Öz**

Tersiyer bir merkez olan kliniğimizde, 2015-2022 yılları arasında doğumu gerçekleşen intra-uterin fetal ölüm vakalarının sıklığını, demografik özelliklerini, risk faktörlerini ve sonuçlarını retrospektif olarak değerlendirmek. Ocak 2015-Aralık 2021 tarihleri arasında Muğla Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde intra-uterin fetal ölüm nedeni ile doğumu gerçekleşen, 22-41 hafta arasındaki, 92 gebe değerlendirildi. Gebelerin başvuru anındaki yaş, gravida, parite, vücut kitle indeksi (VKİ) verileri, gebelik haftaları, doğum sonrası ise doğum ağırlıkları, doğum şekilleri, bebek cinsiyeti ve patolojik inceleme sonuçları kayıt edildi. Belirtilen tarihler arasında 92 intra-uterin fetal ölüm gerçekleşmiştir. Doğum sayısına oranı 1.03% olarak saptanmıştır. 88 (%95.65) tanesi tekil gebelik, 4 (%4.34) tanesi çoğul gebelik idi. Yaş ortalamaları 29.47±5.71 idi. 1'er (%1.08) gebe 18 yaşın altında ve 40 yaşın üzerine idi. VKİ ortalamaları 25.54±3.90 kg/m$^2$ iken, 2 (%2.16) gebenin VKİ'si morbid obez (≥40 kg/m$^2$) seviyesinde izlenmiştir. Gestasyonel yaşları 31.07±4.87 hafta idi. İntra-uterin fetal ölüm nedenleri değerlendirildiğinde, 12 (%13.18) gebede plasenta dekolmanı saptanmıştır. Plasenta dekolmanı saptanan gebelerin 6 (%50)'sinde gebeliğin hipertansif bozuklukları mevcuttu. 5 (%5.49) gebede diabetes mellitus, 2 (%2.19) gebede plasenta previa saptanmıştır. 7 (%7.60) gebenin yatışında uteroplasental yetmezlik bulgusu olan anhidroamniyoz saptandı. 20 (%21.97) gebede fetal anomali izlenmiştir. 1 (%1.09) gebede dissemine intravasküler koagülasyon gelişmiştir. 3 (3.26%) gebede ise COVID-19 saptanmış olup hospitalize edilmiştir. İntra-uterin fetal ölüm vakalarının ön görülebilirliği düşüktür. Fakat bu duruma rağmen, her merkez kendi sonuçlarını değerlendirerek ve risk faktörlerini belirleyerek pro-aktif yaklaşım ile intra-uterin fetal ölüm vakalarını kısmi olarak azaltabilir.

**Anahtar Kelimeler:** Intra-Uterin Fetal Ölüm, Ölü Doğum, Risk Faktörü

**Abstract**

The present study aims to retrospectively analyze the frequency, demographic characteristics, affecting risk factors and outcomes of intra-uterine fetal death (IUFD) cases delivered between 2015 and 2022 in our clinic, a tertiary center. Between January 2015 and December 2021, 92 pregnant women between 22-41 weeks of gestational age who gave birth due to IUFD in Muğla University Education and Research Hospital clinic were included in the study. Age at presentation, gravida, parity and body mass index (BMI) data, gestational weeks, and if after birth, birth weight, mode of delivery, infant sex and pathologic examination results were recorded. There were 92 cases of IUFD between the specified dates. The ratio of cases to the number of births was 1.03%. Of the cases, 88 (95.65%) were singleton pregnancies and 4 (4.34%) were multiple pregnancies. The mean age was 29.47±5.71 years. Among the cases, 1 (1.08%) pregnant woman was under 18 years of age and 1 pregnant woman was over 40 years of age. The mean BMI was 25.54±3.90 kg/m2 and 2 (2.16%) pregnant women were morbidly obese (≥40 kg/m2). The mean gestational age was 31.07±4.87 weeks. When the causes of IUFD were evaluated, placental abruptio1n was observed in 12 (13.18%) pregnant women. Hypertensive disorders of pregnancy were present in 6 (50%) of the pregnant women with placental abruption. While 5 (5.49%) pregnant women had diabetes mellitus, 2 (2.19%) had placenta previa. A total of 7 (7.60%) pregnant women had anhydroamniosis, a sign of uteroplacental insufficiency, during hospitalization, while 20 (21.97%) pregnant women had fetal anomaly. One (1.09%) pregnant woman developed disseminated intravascular coagulation. In addition, 3 (3.26%) pregnant women had COVID-19 and were hospitalized. The predictability of IUFD cases is low. But despite this, each center can partially reduce the incidence of IUFD with a pro-active approach by evaluating its own outcomes and identifying risk factors.

**Keywords:** Intra-Uterin Fetal Death, Stillbirth, Risk Factor

## Introduction

Fetal death is defined by the World Health Organization (WHO) as the death of a fetus prior to the complete removal or abortion of a product of conception from the mother, regardless of the duration of pregnancy (1). However, the main problem with the definition is the difference of opinion on the limit of fetal viability. The WHO considers a fetal weight of 500 g, a gestational age of 22 weeks and a crown-heel length of 25 cm to be the limit (2). In European countries, there are approaches ranging from the 16th to the 26th week of gestation to define it (1). It is difficult to give clear information about the frequency of cases due to differences in definitions, registration systems of countries etc. In addition to studies reporting a prevalence between 0.5% and 1%, there are also studies reporting a prevalence of around 3% (3-5). In our country, WHO criteria are applied and the frequency of cases is 0.9% (6). What is not in dispute, however, is the high incidence of cases in countries in South Asia and Sub-Saharan Africa (3).

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When analyzing the etiologic factors, it is useful to divide them into maternal, fetal and placental factors. Comorbid diseases before and during pregnancy [spectrum of hypertensive diseases, diabetes mellitus (DM)], age, uterine and cervical pathologies, smoking, infections and obesity are the leading maternal factors. Genetics, congenital anomalies and utero-placental anomalies and intra-uterine growth retardation (IUGR) are among the fetal and placental factors (7). However, in some fetal deaths, no cause can be found despite obstetric follow-up and pathology examinations after intra-uterine fetal death (IUFD). This condition is called "Sudden intrauterine unexplained death (SUID)" (8). SUID poses a medicolegal problem for obstetricians and a psychological problem for pregnant women, especially in developed countries.

In the current study, the frequency, demographic characteristics, risk factors and outcomes of IUFD cases delivered in our clinic between 2015-2022 are evaluated retrospectively.

## Material and Method

Between January 2015 and December 2021, a total of 92 pregnant women who delivered due to IUFD in gynecology and obstetrics clinic were included in this study. IUFD was evaluated in proportion to the total number of deliveries between the specified dates. The ethical approval was granted from the Muğla Sıtkı Koçman Hospital ethical committee (Number: 70, Date: 06.09.2022). Since the study was planned retrospectively, no consent form was taken from the participants. All reported research involving "human beings" were conducted in accordance with the principles outlined in the Helsinki Declaration Fortaleza, October 2013. Pregnant women with a gestational age between 22-41 weeks without fetal heartbeat were included in the study. Age at presentation, gravida, parity, body mass index (BMI), gestational age, birth weight, mode of delivery and sex of the baby were recorded. Gestational weeks were determined by correlating the last menstrual date and first trimester ultrasonography data. Women were excluded if any of the following criteria was met: IUFD cases referred from other centers, pregnant women with a gestational age of less than 22 weeks, and pregnant women with unavailable data.

*Statistical Analysis*

The statistical analyses were performed with SPSS 22.0 for Windows program. The Independent Sample T-test was applied for normally distributed data. The results obtained were expressed as mean±SD. The Mann-Whitney U test was applied for non-normally distributed data. The results were expressed as median (min, max) and frequencies and percentages.

## Results

A total of 92 pregnant women who met the inclusion criteria were included in the study. Of these pregnant women, 88 (95.65%) were Turkish citizens, while 4 (4.34%) were foreign nationals. In addition, 88 (95.65%) were singleton pregnancies and 4 (4.34%) were multiple pregnancies. The mean age was 29.47±5.71 years. While 1 (1.08%) pregnant woman was under 18 years of age, 45 (48.91%) pregnant women were between 18-29 years of age, 45 (48.91%) pregnant women were between 30-39 years of age and 1 (1.08%) pregnant woman was 40 years of age or older. The mean BMI was 25.54±3.90 $kg/m^2$ and 42 (45.65%) pregnant women were between 18.5 and 24.9 $kg/m^2$, which is the ideal BMI. Two (2.16%) pregnant women were morbidly obese (≥40 kg/m2). The mean parity of pregnant women was 2.03±1.16. The number of nulliparous patients was 50 (54.34%). A total of 52 (56.52%) fetuses were female. The mean gestational age of the pregnant women was 31.07±4.87 weeks with gestational ages ranging between 22 and 41 weeks. While 19 (20.87%) pregnant women were in the 22-$27^{th}$ gestational week, 58 (63.73%) pregnant women were in the 28-$36^{th}$ gestational week and 15 (16.30%) pregnant women were in the $37^{th}$ or more gestational week. The mean birth weight was 1654.01±947.07 g. While 38 (41.75%) fetuses were between 0-1000 g, 22 (24.17%) fetuses were between 1000-2000 g, 24 (26.37%) fetuses were between 2000-3000 g, 7 (7.69%) fetuses were between 3000-4000 g and 1 (1.08%) fetus was over 4000 g. The demographic characteristics of the pregnant women are shown in Table-1. A total of 52 (56.52%) pregnant women delivered by cesarean section (C/S), while 40 (43.47%) pregnant women delivered vaginally after induction. Dinoposton and Misoprostol were used as induction methods. The most common indications for C/S were previous C/S in 26 (50%) cases and failed induction in 15 (28.84%) cases.

**Table 1.** Demographic characteristics of pregnant women

| | Overall (n=92) |
|---|---|
| **Maternal's Age (year)** | |
| Mean (SD) | 29.47±5.71 |
| Median (Range) | 30.00 (17.00, 40.00) |
| Median (Q1, Q3) | 30.00 (25.00, 34.00) |
| **Parity (n)** | |
| Mean (SD) | 2.03±1.16 |
| Median (Range) | 2.00 (0.00, 5.00) |
| Median (Q1, Q3) | 2.00 (1.00, 3.00) |
| **Gestational week (n)** | |
| Mean (SD) | 31.07±4.87 |
| Median (Range) | 31.00 (22.00, 41.00) |
| Median (Q1, Q3) | 31.00 (28.00, 35.00) |
| **Birth weight (g)** | |
| Mean (SD) | 1654.01±947.07 |
| Median (Range) | 1500.00 (430.00, 4200.00) |
| Median (Q1, Q3) | 1500.00 (800.00, 2210.00) |

A total of 13 (14.13%) pregnant women had the spectrum of hypertensive disorders of pregnancy, including 12 (13.18%) with preeclampsia (PE) and 1 (1.09%) with eclampsia. Besides, 12 (13.18%) pregnant women had placental abruption. Hypertensive disorders of pregnancy were present in 6 (50%) of the pregnant women with placental abruption. While 5 (5.49%) pregnant women had DM, 2 (2.19%) had placenta previa. A total of 7 (7.60%) pregnant women were hospitalized with anhydroamniosis, a sign of uteroplacental insufficiency, while 20 (21.97%) pregnant women had fetal anomaly. Disseminated intravascular coagulation (DIC) developed in 1 (1.09%) pregnant woman. The pregnant woman who had DIC recovered with medical treatment in the anesthesia intensive care unit after delivery. COVID-19 was seen in 3 (3.26%) pregnant women, resulting in their hospitalization. Risk factors for IUFD are presented in Table 2.

**Table 2.** IUFD risk factors

| Risk Factor | Proportion n (%) |
|---|---|
| Unknown cause | 29 (31.52%) |
| Fetal Anomaly | 20 (21.97%) |
| Preeclampsia / eclampsia | 13 (14.13%) |
| Placental abruption | 12 (13.18%) |
| Anhydroamnios | 7 (7.60%) |
| Diabetes Mellitus | 5 (5.43%) |
| Uteroplacental Insufficiency | 3 (3.26%) |
| COVID-19 | 3 (3.26%) |
| Placenta Previa | 2 (2.17%) |
| Disseminated Intravascular Coagulation | 1 (1.08%) |

## Discussion

In the present study, a total of 92 cases of IUFD in our clinic between January 2015 and December 2021 were retrospectively evaluated.

In the study by DeGraaf et al. the prevalence of IUFD was found to be 0.7% (9). In the study by Sharma et al. it was found to be 3.6%. A history of IUFD was present in 9.2% of these pregnant women (10). Congenital malformations were present in 8.8% of the infants. Hydrocephalus and anencephaly were the most common congenital anomalies. In the study by Ohana et al. the prevalence of IUFD was found to be 7.4% (11). The biggest risk factor has been shown as "previous adverse perinatal outcome". The prevalence of IUFD in the hospital was found to be 1.03%. In a review study of IUFD cases, Wojcieszek et al. blamed infections in 5%-22%, congenital anomalies in 6%-22%, and unexplained causes in up to 76% of the cases (12). In the present study, fetal anomaly was the most common cause with 20 (21.73%) cases. We think that the most important reason why the prevalence of IUFD in the literature is quite different is related to the health registration system. We think that another important reason is the differences in perinatal follow-up frequencies.

The most common fetal anomalies were hydrocephalus and anencephaly with 10 (50%) cases. Unexplained causes were at a rate of 31.52%. This rate is consistent with the literature. The inconsistent result with the literature is that IUFD due to infection was not observed. The reason for this situation is that only toxoplasma, rubella and CMV IgM screening is performed at the beginning of pregnancy in our clinic. The fact that fetuses and stillbirths are not examined for infectious diseases is a shortcoming of our clinic. The increased risk of fetal loss in pregnant women infected with COVID-19 has been attributed to the predisposition of COVID-19 infection to thromboembolic events (13). Data collection for the current study started in 2015 and COVID-19 infection emerged in 2019. Therefore, it is not accurate to give rates regarding IUFD.

There is a correlation between the gestational week at which IUFD occurs and the causes of IUFD (14). Especially in pregnant women with a history of IUFD, preventability can be achieved with a proactive approach in subsequent pregnancies. Patient data on history of IUFD was not available and this is a limitation of the present study. While events associated with infection and congenital anomalies occur at earlier gestational weeks, causes such as hypertensive disorders of pregnancy and post-term are seen at later gestational weeks. When the timing of delivery was evaluated in the study by Monacho et al., 65% IUFD occurred in early preterm (PT) (<34 weeks), 20% in late PT (34 weeks to 37 weeks) and 15% in term (>37 weeks) period (3). In the study by De Graaf et al. the timing of delivery was found to be 30.68±0.66 weeks (9). In the study by Sharma et al. 47.2% of IUFD cases occurred in preterm and 52.8% in term period (10). In the study by Ohana et al, this was found to be 32.0+5.62 weeks. A total of 28.7% of cases were at term period (11). In the present study, the mean gestational age was 31.07±4.87 weeks. While 19 (20.87%) pregnant women were in the 22-27$^{th}$ gestational week, 58 (63.73%) pregnant women were in the 28-36$^{th}$ gestational week and 15 (16.30%) pregnant women were in the 37$^{th}$ and above gestational week. The results of the study are similar to those obtained in the study by Monacho et al. and are consistent with the current literature. It is considered that the most appropriate method for partial prevention of IUFDs between 28-36 weeks and at term is fetal movement monitoring. Randomized controlled studies should be conducted on the subject.

The birth weight of an IUFD fetus is correlated with the gestational week at the time of fetal loss. This may change only in pregnant women with fetal growth restriction (15). In the study by De Graaf et al. the mean weight of infants with IUFD was found to be 1738.47±112.31 g (9). In the study by Sharma

et al., 26% of stillborn fetuses had a birth weight between 2001-2500 g (10). Fetuses weighed between 1501-2000 g and 2501-3000 g in descending order. In the present study, the mean birth weight was 1654.01±947.07 g and 41.75% of the fetuses were in the 0-1000 g range. These results are consistent with the current literature. The relationship between fetal gender and fetal loss has been a subject of curiosity in the literature. In the study by Monacho et al., the ratio of male:female fetuses was found to be 1:1.7 (3). In the study by De Graaf et al., 52.3% of fetuses were female (9). In the present study, however, fetuses were female at a ratio of %56.52. These results are consistent with those in the literature.

From the moment the diagnosis of IUFD is made, the mode and timing of delivery becomes important. The risk of DIC is correlated with the time the products of conception spend as intra-uterine (16). The mode of delivery is important in terms of morbidity and the pattern of subsequent deliveries. In the study by Sharma et al., 70.8% of fetuses with IUFD were born with vaginal delivery (10). In the study by Ohana et al. 9.4% of deliveries occurred by C/S (11). In the present study, the rate of C/S delivery was 56.52%. The most common indication for C/S was previous C/S in 26 (50%) and failed induction in 15 (28.84%). This rate is much higher than other studies. When evaluating the C/S rate, it is necessary to take into consideration the frequency of pregnant women who have had previous C/S deliveries due to the increased C/S rate in our country (17,18).

Factors such as PE, hypertensive disorders of pregnancy such as eclampsia, spectrum of DM, oligohydramnios are partially preventable factors for IUFD (19). In the study by Monacho et al. PE was 39%, abruptio placentae was 4%, oligohydramnios 5%, and pregestational DM/GDM A1/GDM A2 were 2%/3%/2% (3). In the study by De Graaf et al, however, 10.9% pregnant women had pre-gestational DM, 11.6% had GDM, 3.1% had PE, and 4.7% pregnancy hypertension (9). In the study by Sharma et al., 14.4% had gestational hypertension, 8% had PE, and 8.4% had eclampsia (10). In the present study, however, 14.13% pregnant women had PE/eclampsia, 5.43% had DM, 13.04% had placental abruption, and 4.34% anhydramnios. Although there are no preventive methods in pathologies other than DM, it is important to follow up in the light of the recommendations of the guideline. This was proven by the study by Kafadar et al. (20). In cases where IUFD occurs, fetal autopsy is considered the "gold standard" method to determine the cause of IUFD (21). Encouraging parents to perform fetal autopsy and examination of the placenta will lead to more accurate results and save the obstetrician from medico-legal problems. Fetal autopsy is not accepted by parents due to some cultural or religious beliefs. In such cases, partial autopsy, imaging methods and genetic examinations are recommended (12).

The risk of IUFD is 50% higher among pregnant women aged 15-19 years (22). There is also an increased risk from the age of 35, although it is higher over the age of 40 (23). In the study by Monacho et al. the mean maternal age was 26 years (18–36 years) (3). In the study by De Graaf et al., however, this was found to be 27.98±0.51 (9). In the study by Ohana et al., the maternal age was found to be 29.28+6.73 and it was between the age range of 19-29 at a rate of 50.9% (11). In the present study, the mean age of women with IUFD was 29.47±5.71. Only 1 (%1.08) pregnant woman was under the age of 18 and 1 was over the age of 40. In the study by Monacho et al., the mean BMI was found to be 27.98±0.67 kg/m$^2$ (3). The increased BMI category was associated with an increased risk of IUFD. The riskiest group was identified as morbidly obese (≥40 kg/m$^2$). While the BMI mean of the pregnant women included in this study was 25.54±3.90 kg/m$^2$, it was seen that 2 (%2.16) pregnant women were morbid obese. It is considered that prenatal outcomes may improve with weight control, especially in the pre-gestational stage, in pregnant women with a history of IUFD and in pregnant women with DM, GDM or obese women.

In the studies carried out other risk factors for IUFD are stated to include smoking, primiparity, multiple pregnancies, post-term pregnancy, etc. (12, 24). In this study, 54.34% of pregnancies were primiparous and 4.34% were multiple pregnancies. Being primiparous is not a changeable condition. However, it is very important that these pregnant women are informed about the situation during follow-up and delivery processes. The definition and approach to post-term pregnancy remains controversial (25). In our clinic, elective induction is performed in pregnant women who reach 41 weeks of gestation. Patient data on smoking was not available and this is a limitation of the present study.

Evaluating the results of our clinic, which is the only tertiary central hospital in our province, for a long period of 7 years is a strong aspect of our study.

## Conclusion

In conclusion, due to their low predictability, IUFD cases are medico-legal for obstetricians and physiologically and psychologically harmful for pregnant women. Each clinic can partially reduce this situation with a pro-active approach by evaluating its own outcomes and identifying risk factors. However, especially high-risk pregnant women should be informed that this situation cannot be prevented to a large extent.

One of the limitations of our study is that perinatal infections could not be evaluated. Another limitation is the retrospective design of the study.

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Regarding the limitations of our study, this was a retrospective review with a small sample size in a single center in a restricted region.

## Conflict of interest statement

Authors declare that there is no conflict of interest between the authors of the article.

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of the Muğla Sıtkı Koçman University (06.09.2022, No:70).

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