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Evaluation of obstetric outcomes and risk factors of early late and term stillbirths

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Abstract

Objective: Stillbirth is defined as the death or loss of the fetus before or during birth in pregnancies over the 20th week of gestation. The aim of our study is to determine the risk factors for stillbirth and to compare the obstetric and maternal outcomes of early, late and term stillbirth cases.

Methods: Our retrospective case-control study included pregnant women, between the ages of 18 and 45, who had a stillbirth over the 20th week of gestation, between February 1, 2015 and June 31, 2023. Patients were compared considering of demographic characteristics and obstetric outcomes.

Results: Parity≥3 (OR 0.34; 95% CI: 0.15–0.78. p = 0.011), abruptio placentae (OR 0.29; 95% CI: 0.04–0.51, p = 0.009), preterm birth (OR 0.35; 95% CI: 0.16–0.74, p = 0.006), LBW (OR 0.09; 95% CI: 0.04–0.23, p = 0.001), oligohydramnios OR 0.16; 95% CI: 0.03–0.27, p = 0.001) were associated with stillbirth in multivariate analysis. The caesarean section rate and the presence of small for gestational age were found to be statistically lower in the early group. (p=0.01, p=0.029 respectively).The presence of breech presentation was found to be statistically significantly lower in the term group (p=0.0001).

Conclusion: Risk factors associated with stillbirth include preterm birth, low birth weight, abruptio placentae, oligohydramnios and parity 3 and above. When early, late and term groups were compared, the caesarean section rate and the presence of small for gestational age were found to be statistically lower in stillbirths under 28 weeks.

Keywords: Stillbirth, abruptio placentae, small for gestational age, oligohydramnios

Introduction

Stillbirth is defined as the death or loss of the fetus before or during birth in pregnancies over the 20th week of gestation. An antepartum fetal loss is a death that occurs before the onset of labor; however intrapartum fetal death occurs during birth and therefore may not show signs of maceration. Pregnancy termination due to fetal anomalies is not included in the terminology of stillbirth.[1] The World Health Organization (WHO) defines stillbirth as a newborn with no signs of life at birth at a gestational age greater than 28 weeks.[2] Stillbirth is a significant psychosocial problem and the estimated stillbirth rate in the United States is 6 per 1000 births.[3]

In high-income countries, congenital, anatomical or karyotype abnormalities, placental problems associated with growth restriction, and maternal medical illnesses are common causes of stillbirth; whereas prolonged labor, preeclampsia, and infection-related stillbirths are more common in low-income countries. While approximately 6% of stillbirths occur in the intrapartum period in developed countries, this rate rises to 50% in developing countries due to the limited number of centers where cesarean section is performed.[4]

Increasing prenatal care opportunities and easier access to health services have led to a decrease in stillbirth rates over time. But the risk of stillbirth in subsequent pregnancies is approximately five times higher in women who had a stillbirth in their first pregnancy, compared to women who had a live birth.[5] Socioeconomic deprivati-

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on and domestic violence have been also associated with late stillbirth.[6]

Compared to singleton pregnancies, the risk of stillbirth increases 2.5 times in twin pregnancies.[7] Maternal age under 25 or over 35years, black race, smoking, alcohol, substance use, obesity, unmarried status, environmental high temperature, low socioeconomic status, antepartum hemorrhage and pre-existing diabetes, are also risk factors for stillbirth.[8,9] The aim of our study is to determine the risk factors for stillbirth and to compare the obstetric and maternal outcomes of early, late and term stillbirth cases.

Methods

Our retrospective case-control study included pregnant women, between the ages of 18 and 45 years, who had a stillbirth over the 20th week of gestation at Obstetric Department of Prof. Dr. Cemil Taşçıoğlu City Hospital between February 1, 2015 and June 31, 2023 Apgar scores of 0 at 1 and 5 minutes and no signs of life by direct observation.

Gestational age was calculated according to the date of the last menstrual period or ultrasound findings. The exclusion criteria were as follows: multiple pregnancies, smoking, alcohol and substance use, maternal age of <18 years, pregestational diabetes, pregnancy termination due to known fetal anomaly and intrapartum stillbirth. Hospital records were reviewed for information on patients who had stillbirths and pregnant women who had live births on the same day as these patients. The absence of fetal heartbeat in all stillbirth cases was determined ultrasonographic examination.

Patients were compared considering maternal age, delivery type, gravida, parity, abortus, presentation, hemoglobin, hematocrit, fetal weight, gestational age of birth, gender, maternal intensive care need, Assisted Reproductive Technology (ART), placenta previa, preeclampsia, gestational diabetes (GDM), placental abruption, small for gestational age (SGA), preterm birth, post-term birth, preterm premature rupture of membrane (PPROM), prematüre rupture of membrane (PROM), low birth weight (LBW), macrosomia, oligohydramnios, polyhydramnios and fetal anomaly.

As recommended by the United States National Center for Health Statistics; fetal loss at ≥20 weeks' gestation was classified as early stillbirth (20 to 27 completed weeks), late stillbirth (28 to 36 completed weeks), and term stillbirth (≥37 completed weeks).[1] Maternal and obstetric outcomes were compared between these three groups. This study complies with the Declaration of Helsinki. The Ethics Committee of Health Science University, Prof. Dr. Cemil Taşçıoğlu City Hospital, approved the study (Date.28/08/2023 /No. E-48670771-514.99-223229108).

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In the evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation, median, interquartile range), the distribution of the variables was examined with the Shapiro - Wilk normality test, one-way analysis of variance in comparisons between normally distributed variables, Tukey's multiple comparison test in subgroup comparisons, Independent t-test was used for comparison, Kruskal Wallis test was used for intergroup comparisons of variables that did not show normal distribution, Dunn's multiple comparison test was used for subgroup comparisons, Mann Whitney U test was used for comparison of paired groups, and chi-square and Fisher reality test were used for comparisons of qualitative data. Univariate and Multivariate results were evaluated at the significance level of $p<0.05$ to determine the factors affecting the presence of stillbirth.

Results

For nine years, there were 287 stillbirths out of 22715 deliveries (1.263%). The patients who have exclusion criteria were not included in the study. For each case, one control was recruited and matched according to criteria such as day of delivery. Pregnant women who gave birth to stillbirth were classified as group 1(n:168); pregnant women who gave live birth on the same date were classified as group 2 (n:168). Demographic characteristics and obstetric outcomes were compared between the two groups (Table 1).

The mean maternal age of group 1 cases was 28.7±6.93 year and in group 2 it was 27.17±7.42 years, and no significant difference was detected between the two groups. But the mean gravida and parity were significantly higher in group 1 (p= 0.046, p= 0.033 respectively). While there was no significant difference in nulliparity, the stillbirth rate was significantly higher in patients with parity ≥ 3 (p= 0.015). Mean fetal weight was statistically significantly lower in Group 1 (1941.28±1007.28 g) as compared to Group 2 (3167.29±501.89 gr) (p= 0.0001). The mean gestational week was 32.8±5.12 in group 1; It was found to be 38.08±1.92 in group 2. This difference is statistically significant (p= 0.0001). No cause was detected in 63 of our 168 stillbirth patients. The rate of unexplained stillbirth was 37.5%.

Table 1. Demographic characteristics and obstetric outcomes in stillbirth

		Group 1 Stillbirth n:168		Group 2 Control n:168		p
Age (years)	**Mean (SD)**	28.7±6.93		27.17±7.42		0.055*
	21-34	101	60.12%	88	52.38%	0.06+
	≤20	28	16.67%	46	27.38%	
	≥35	39	23.21%	34	20.24%	
Delivery	**Vaginal**	95	56.55%	96	57.14%	0.912+
	Cesarean	73	43.45%	72	42.86%	
Gravida	**Mean (SD)**	2.94±1.84		2.51±1.48		0.046‡
	Median (IQR)	3 (2-4)		2 (1-3)		
Parity	**Mean (SD)**	1.6±1.55		1.21±1.26		0.033‡
	Median (IQR)	1 (0-2)		1 (0-2)		
Abortus	**Mean (SD)**	0.33±0.75		0.31±0.58		0.519‡
	Median (IQR)	0 (0-0)		0 (0-0.75)		
Parity ≥3		38	22.62%	21	12.50%	0.015+
Nulliparity		48	28.57%	59	35.12%	0.198+
Presentation	**Cephalic**	140	83.33%	161	95.83%	0.0001+
	Breech	28	16.67%	7	4.17%	
Hemoglobin	**Mean (SD)**	11.46±1.92		11.26±1.53		0.274*
Hematocrite	**Mean (SD)**	34.64±5.1		33.81±4.67		0.123*
Fetal weight (gr)	**Mean (SD)**	194.28±1007.28		3167.29±501.89		0.0001*
Gestational age (weeks)	**Mean (SD)**	32.8±5.12		38.08±1.92		0.0001*
ART	**-**	167	99.40%	167	99.40%	1ǂ
	+	1	0.60%	1	0.60%	
Gender	**Female**	77	45.83%	82	48.81%	0.585+
	Male	91	54.17%	86	51.19%	
Placenta Previa		3	1.79%	2	1.19%	0.652+
MICU		13	7.74%	0	0.00%	0.0001ǂ
SGA		44	26.19%	5	2.98%	0.0001+
GDM		7	4.17%	9	5.36%	0.608+
Preeclampsia		46	27.38%	10	5.95%	0.0001+
Placental abruption		41	24.40%	3	1.79%	0.0001+
Preterm birth		129	76.79%	36	21.43%	0.0001+
Postterm birth		6	3.57%	2	1.19%	0.152ǂ
LBW		119	70.83%	13	7.74%	0.0001+
Macrosomia		3	1.79%	5	2.98%	0.474ǂ
Oligohydramnios		29	17.26%	5	2.98%	0.0001+
Polyhidramnios		4	2.38%	3	1.79%	0.702ǂ
Fetal anomaly		11	6.55%	1	0.60%	0.003ǂ
PPROM		3	1.79%	9	5.36%	0.078ǂ
PROM		4	2.38%	9	5.36%	0.157ǂ

*Independent t test ‡Mann Whitney U test + Chi-Square test ǂFisher's Exact Test

SGA:Small for gestational age, GDM:Gestational Diabetes Mellitus, PROM :Premature rupture of membrane, PPROM:Preterm premature rupture of membrane, LBW: Low birth weight
ART: Assisted Reproductive Technology MICU Maternal intensive care unit

When two groups were compared; Preeclampsia, placental abruption , Maternal intensive care unit admission, small for gestational age (SGA), preterm birth, low birth weight(LBW), oligohydramnios, breech presentation and fetal anomaly were seen statistically significantly higher in group 1.

Parity ≥3 (OR 0.49; 95% CI: 0.27–0.88, p = 0.016), breech presentation (OR 0.22; 95% CI: 0.09–0.52, p = 0.001), SGA (OR 0.09; 95% CI: 0.33–0.22, p = 0.010), preeclampsia (OR 0.17; 95% CI: 0.08–0.35, p = 0.001), placental abruption (OR 0.06; 95% CI: 0.02–0.19, p = 0.001), preterm birth (OR 0.08; 95% CI: 0.05–0.14, p = 0.001), LBW (OR 0.04; 95% CI: 0.02–0.07, p = 0.01), oligohydramnios (OR 0.15; 95% CI: 0.06–0.40, p = 0.001) were associated with stillbirth in univariate analysis (Table 2).

Multivariate analysis was then performed with all significant (as determined by univariate analysis above) risk factors. The adjusted variables for conducting multivariate analysis were Parity ≥3 , breech presentation, SGA, preeclampsia, placental abruption, preterm birth, LBW, and oligohydramnios.

Parity ≥3 (OR 0.34; 95% CI: 0.15–0.78, p = 0.011), placental abruption (OR 0.29; 95% CI: 0.04–0.51, p = 0.009), preterm birth (OR 0.35; 95% CI: 0.16–0.74, p = 0.006), LBW (OR 0.09; 95% CI: 0.04–0.23, p = 0.001), oligohydramnios (OR 0.16; 95% CI: 0.03–0.27, p = 0.001) were associated with stillbirth in multivariate analysis (Table 2).

Early, late and term groups were compared in terms of demographic characteristics and obstetric outcomes (Table 3). The caesarean section rate and the presence of SGA were found to be statistically lower in the early group (p=0.01, p=0.029 respectively). The presence of breech presentation was found to be statistically significantly lower in the term group (p=0.0001).

Table 2. Univariate and Multivariate Logistic Regression

	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (OR %95 CI)	p	OR (OR %95 CI)	p
Parity≥3	0.49 (0.27-0.88)	**0.016**	0.34 (0.15-0.78)	**0.011**
Breech	0.22 (0.09-0.52)	**0.001**	0.53 (0.15-1.86)	**0.318**
MICU	0.01 (0.002-0.03)	**0.967**		
SGA	0.09 (0.33-0.22)	**0.010**	0.58 (0.14-1.85)	**0.309**
Preeclampsia	0.17 (0.08-0.35)	**0.001**	1.28 (0.26-3.44)	**0.764**
Placental abruption	0.06 (0.02-0.19)	**0.001**	0.29 (0.04-0.51)	**0.009**
Preterm birth	0.08 (0.05-0.14)	**0.001**	0.35 (0.16-0.74)	**0.006**
LBW	0.04 (0.02-0.07)	**0.01**	0.09 (0.04-0.23)	**0.001**
Oligohydramnios	0.15 (0.06-0.40)	**0.001**	0.16 (0.03-0.27)	**0.001**
Fetal anomaly	0.09 (0.01-0.67)	**0.190**		

MICU Maternal intensive care unit, SGA:Small for gestational age, LBW: Low birth weight

Table 3. Comparison of demographic characteristics and obstetric outcomes of early, late and term stillbirths

		Early n:34		Late n:95		Term n:39		p
Age(years)	**Mean (SD)**	28.44±7.37		28.59±6.76		29.21±7.11		0.871‡
	21-34	20	58.82%	57	60.00%	24	61.54%	
	≤ 20	7	20.59%	16	16.84%	5	12.82%	
	≥35	7	20.59%	22	23.16%	10	25.64%	0.927+
Gravida	**Mean (SD)**	3.15±1.65		2.77±1.66		3.18±2.34		
	Median (IQR)	3 (2-4)		2 (1-4)		2 (1-4)		0.188†
Parity	**Mean (SD)**	1.68±1.47		1.48±1.47		1.79±1.79		
	Median (IQR)	1.5 (1-2)		1 (1-2)		1 (0-2)		0.394†
Abortus	**Mean (SD)**	0.44±0.93		0.27±0.68		0.36±0.78		
	Median (IQR)	0 (0-1)		0 (0-0)		0 (0-0.75)		0.542†
Delivery	**Vaginal**	27	79.41%	47	49.47%	21	53.85%	
	Cesarean	7	20.59%	48	50.53%	18	46.15%	0.01+
Parity ≥3		7	20.59%	20	21.05%	11	28.21%	0.635+
Primipar		7	20.59%	30	31.58%	11	28.21%	0.476+

Hemoglobin	**Mean (SD)**	10.95±1.86		11.66±2.04		11.42±1.62		0.181‡
Hematocrit	**Mean (SD)**	33.23±4.93		35.19±5.29		34.52±4.65		0.155‡
	Cephalic	22	64.71%	80	84.21%	38	97.44%	
Presentation	**Breech**	12	35.29%	15	15.79%	1	2.56%	0.001+
ART		0	0.00%	1	1.05%	0	0.00%	0.679+
	Female	11	32.35%	48	50.53%	18	46.15%	
Gender	**Male**	23	67.65%	47	49.47%	21	53.85%	0.189+
Placenta Previa		2	5.88%	1	1.05%	0	0.00%	0.119+
MICU		2	5.88%	8	8.42%	3	7.69%	0.893+
SGA		4	11.76%	32	33.68%	8	20.51%	0.029+
GDM		0	0.00%	4	4.21%	3	7.69%	0.260+
Preeclampsia		6	17.65%	31	32.63%	9	23.08%	0.192+
Placental abruption		7	20.59%	25	26.32%	9	23.08%	0.781+
Oligohydramnios		6	17.65%	13	13.68%	10	25.64%	0.250+
Polihydramnios		0	0.00%	3	3.16%	1	2.56%	0.582+
Fetal anomaly		4	11.76%	5	5.26%	2	5.13%	0.387+

‡ One-Way Variance Analysis, †Kruskal Wallis Test +Chi-Square test
SGA:Small for gestational age, GDM:Gestational Diabetes Mellitus,
ART: Assisted Reproductive Technology MICU Maternal intensive care unit, early stillbirth (20 to 27 completed weeks), late stillbirth (28 to 36 completed weeks), and term stillbirth (≥37 completed weeks).

Discussion

Stillbirth is a major healthy problem worldwide. This study examined various obstetric risk factors and their relationship with stillbirth in a tertiary hospital. Preeclampsia, placental abruption, preterm birth, oligohydramnios, low birth weight and parity 3 and above have the highest risk of stillbirth and the average stillbirth rate in our hospital was 12 per 1000 births. In the study of MacDorman MF et al., they stated that the risk of fetal loss increased in teenagers and pregnant women over the age of 35 years, and that the rate of stilbirth was lowest between the ages of 25-34.[10] When stillbirth and live birth were compared in our study, no significant difference was found in the mean maternal age between the two groups. When the age distributions were examined, 23.21% of those who had stillbirths were 35 years old and over. This result was not compatible with the literature.

Gravida and parity were higher in our patients who had stillbirth. In the study of Gardosi J et al., multivariable analysis identified a significant risk of stillbirth for parity (para 0 and para ≥ 3).[11] While no significant difference was found between the two groups in nulliparity in our study, the risk of stillbirth was significantly higher in patients with parity 3 and above, consistent with the literature.

Approximately 50 percent of stillbirths occur between 20 and 27 weeks of gestation.[10] Whereas, in our study, 20.23% of stillbirths were in early stage; 79.77% were seen over 28. gestational weeks. The average week of birth in the entire stillbirth group was 32.8±5 weeks. Making the decision to give birth in a healthy pregnancy is not always easy. In a study including high-income countries, the prospective risk of stillbirth was 0.11 per 1000 pregnancies at 37 weeks; It was found to be 3.18 per 1000 pregnancies at 42 weeks.[12] In our study, although post-term birth was more common in the stillbirth group, no statistically significant difference was found when compared to live births. In the study of Mondal et al., the crude rate in male fetus was 6.23 stillbirths per 1000 total births, and the risk of stillbirth increases by 10% in male fetuses. [13] Although stillbirth was more common in male fetuses in our study, no statistically significant difference was found when compared to live birth.

The risk of stillbirth is higher with assisted reproductive technologies (ART). However, there is not enough evidence to show whether this risk is related to infertility or to in vitro techniques.[14] In our study, it was not possible to make a comparison, because the number of ART patients was very low and most of our patients had spontaneous pregnancies.

While the causes of fetal deaths seen in the early stages of pregnancy are generally maternal medical conditions, congenital anomalies, fetal growth and development retardation and infections; the cause of late-term deaths may be placental abruption, placenta previa, maternal causes or complications that may occur during birth.[15] In our study, fetuses with fetal anomalies were more common in early fetal losses below 28 weeks. However, fetal death

due to infection has never been observed. In late and term fetal deaths, the rate of fetal death due to preeclampsia and placental abruption was higher, consistent with the literature. In a study by Man J, et al., although autopsy reports were examined, the cause of stillbirth could not be explained. This rate varies between 30% and 60%.[16] The unexplained stillbirth rate in our clinic was 37.5%. In general, it is recommended for patients who have previously had a stillbirth to give birth before the estimated delivery date in order to provide psychological security. However, there is no consensus on this issue.

The fetal anomaly rate in the stillbirth group was found to be 6.55% in our study, This rate is significantly higher compared to live births and fetal anomaly encountered more common in pregnancies under 28 weeks. In a study examining all antenatal fetuses with congenital anomalies, the average stillbirth rate was found to be 2.68%.[17] However, there is less information about genetic causes other than aneuploidy and familial aggregation of stillbirth.[18]

Diabetic pregnant women constitute a risky pregnancy group in terms of adverse perinatal outcomes. The risk of stillbirth in patients treated with insulin has been reported to be 6-35 per 1000 births and gestational diabetes mellitus (GDM) negatively affects 8% of all pregnancies. Vasculopathy in hyperglycemic pregnant women may be associated with decreased uteroplacental perfusion and stillbirth in advanced maternal age or obesity. Approximately 4% of all stillbirths are associated with diabetes.[3,19] The rate of GDM in patients with stillbirth was observed as 4.17% in our study, whereas there was no statistical difference between the stillbirth and live birth groups.

Umbilical cord anomalies such as knot, stricture, and torsion may disrupt fetal microcirculation and cause stillbirth in the third trimester. They were held responsible for 19% of 500 fetal deaths. However, after investigating all causes of fetal death, umbilical cord anomalies may be associated with fetal death.[20] True nodes were observed in only two patients in our study group. These patients were in the last trimester, consistent with the literature. There were no risk factors to explain stillbirth. However, since the number of our cases with cord knots is very low, it is controversial whether the real cause of stillbirth is related to the knot.

Placental abruption and insufficiency are the main causes of fetal death in patients with hypertension. Abruption occurs in about 1 percent of pregnancies but accounts for 10 to 20 percent of all stillbirths. The risk of stillbirth is highest when the separation involves the central part of the placenta and when more than 50 percent of the placental surface has separated.[21] In the study of Egbe TO et al., the risk of stillbirth was more than three times higher in women with preeclampsia. Additionally, the risk of stillbirth was 21 times higher in women with placental abruption.[22] In our study, the preeclampsia was observed in 27.38%; the abruption was observed in 24.40% of stillbirth pregnancies and preeclampsia and placental abruption were associated with stillbirth in univariate analysis. Whereas placental abruption was associated with stillbirth in multivariate analysis. Although preeclampsia and abruption were more common in fetuses over 28 weeks, no significant difference was found for preeclampsia and abruption when the early, late and term stillbirth groups were compared,

Patients who gave birth prematurely or gave birth to an small for gestational age (SGA) baby in their previous pregnancies have an increased risk of giving birth to a stillborn baby in their next pregnancy.[23] If SGA is not detected in the antenatal period, the risk of stillbirth was found to be 19.8 per 1000 births.[11] In our study, the rate of SGA fetuses was significantly higher in the stillbirth group and SGA was associated with stillbirth in univariate analysis according the literature. But the presence of SGA was found to be statistically lower in the early stillbirth stage.

Premature babies were approximately three times more likely to be stillborn than full-term babies.[22] Similar the literature, 76.79% of the patients who had a stillbirth and 21.43% of the pregnant women who had a live birth had a preterm birth in our study. Premature birth was associated with stillbirth in multivariate analysis. Low birth weight (LBW) babies are also at risk of stillbirth. They were five times more likely to have a stillbirth than normal weight babies.[22] LBW was seen statistically significantly higher in stillbirth in our clinic. (70.83% in stillbirth group)

A study by Figueroa L et al., showed that the rate of stillbirth was five fold higher in oligohydramnios patients in low-middle income countries.[24] Consistent with the literature, oligohydramnios was associated with stillbirth in multivariate analysis in our study. However, when early, late and term stillbirth groups were compared, no significant difference was detected in oigohydramnios.

We acknowledge that this study has some limitations. The best way to demonstrate the pregnancy outcomes is to include all live birth cases. But we compared the same number of live birth and stillbirth patients. The placenta was not examined pathologically and a fetal autopsy was not performed. The karyotype analysis was not performed on fetuses with stillbirth. Data related to socioeconomic status, race and ethnicity were not analyzed in this study.

Our study differs from previous studies, with a large

patient group, where we examined the comparision of demographic characteristics and obstetric outcomes in early, late and term stages of stillbirts.

Conclusion

Early recognition and prevention of risk factors are important steps in reducing the number of stillbirths. Risk factors associated with stillbirth include preterm birth, low birth weight, placental abruption, oligohydramnios and parity 3 and above. When early, late and term groups were compared, the caesarean section rate and the presence of SGA were found to be statistically lower in stillbirths under 28 weeks. More research is needed to diagnose poor obstetric outcomes and evaluate effective interventions to reduce stillbirth rates.

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