

The risk factors and maternal adverse outcomes of stillbirth

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Ethics Committee Approval

This study was approved by the Bursa Yuksek
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All procedures in this study involving human
participants were performed in accordance with
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amendments.

Conflict of Interest

No conflict of interest was declared by the
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Abstract

Background/Aim: Stillbirth is a devastating complication of the pregnancy. Contemporary studies have exposed several reasons; however, most of the cases are still unexplained. Stillbirth delivery could cause various maternal complications. We aimed to evaluate the maternal complications and reveal the risk factors for stillbirth.

Methods: A case-control study was performed at a high-volume university-affiliated research and training hospital between June 2016 and June 2020. The study population was divided into two groups as women who delivered stillbirth (study group) and live birth (control group). Patients' characteristics, birth weight and gender of the newborn, hospital stay, delivery type, concomitant diseases in pregnancy such as preeclampsia, gestational diabetes mellitus, fetal anomaly, preterm premature rupture of the membranes and complications such as uterine atony, abruptio placenta, postpartum hemorrhage, disseminated intravascular coagulation, and uterine rupture were evaluated from the medical records and compared between groups.

Results: A total of 46019 births occurred during the study period. The number of women who delivered stillbirth was 520 with a rate of 11.2 per 1000 births. The control group included 6521 patients. Comparison of the groups revealed that women delivering stillbirth were older ($P<0.001$), had longer hospital stay ($P<0.001$), lower newborn birth weight ($P<0.001$), and more babies with congenital anomalies ($P<0.001$) than the control group. The women in stillbirth group experienced more preterm premature rupture of the membranes ($P<0.001$), preeclampsia ($P<0.001$), gestational diabetes mellitus ($P<0.001$), abruptio placenta ($P<0.001$), postpartum hemorrhage ($P<0.001$), and disseminated intravascular coagulation ($P<0.001$). The rates of severe obstetric and postpartum complications were 14.2% and 12.1%, respectively. Multivariate logistic regression analysis revealed that fetal anomaly (OR 3.170; 95% CI 1.592-6.315, $P<0.001$), gestational diabetes mellitus (OR 15.203; 95% CI 8.368-27.621, $P<0.001$) and abruptio placenta (OR 18.221; 95% CI 9.121-36.402, $P<0.001$) increased the risk of stillbirth.

Conclusion: Stillbirth delivery could lead to severe maternal complications that can threaten maternal vitality. Close delivery follow-up is essential, especially during the early postpartum period. Care should be taken for postpartum complications such as disseminated intravascular coagulation and postpartum hemorrhage. Furthermore, patients should be examined carefully for abruptio placenta. Stillbirth deliveries should be carried out in fully equipped hospitals.

Keywords: Abruptio placenta, Gestational diabetes mellitus, Maternal complication, Stillbirth

Introduction

Stillbirth can be assumed as the most dramatic end of the fairytale. Patients, physicians, and all health care providers are affected by the consequences of stillbirth. Even a live birth could cause trauma and depression, bereavement of the baby may lead to serious psychological, economical, biological outcomes. Therefore, stillbirth rates are as important as maternal mortality rates, which is considered one of the most important general indicators of the health system. An underestimated topic, it is the problem of the low and middle-income countries, especially African countries. It has been stated that about 98% of stillbirths occur in these countries. However, this percentage could be the seen part of an iceberg, because stillbirth definition involves a baby born with no signs of life at or after 28th week of gestation with a birth weight of ≥ 1000 g [1,2]. The definition varies especially in developed countries in terms of the gestation week (≥ 20 weeks or 22 weeks) and birth weight (≥ 350 gr or 500gr) [3,4]. The incidence of stillbirth in America was 5.96 in 1000 live births. Almost half were born before the 28th week of gestation and the rates tend to decrease compared to previous years [5]. The evolution of medicine and increased opportunities had an essential role in decreasing stillbirth rates. Women with diabetes used to experience stillbirth by approximately 65% in the 1920s however, patients with advanced glycemic control carry almost the same risk as those without diabetes [6,7]. Similarly, adequate treatment of preeclampsia (PE), hypertensive disorders, Rhesus alloimmunization, intrauterine growth restriction, preterm premature rupture of membranes (PPROM), and infections had also essential roles in decreasing stillbirth rates.

Despite these interventions, stillbirth is still a devastating obstetric complication. Management of stillbirth delivery is also a compelling issue. Two of the three components of the labor- the 3Ps, passageway, passenger, and power, are defective. Many women's labor would start and end within 1 or 2 weeks of fetal demise spontaneously, however, if the expectant interval prolongs more than 3 weeks, disseminated intravascular coagulation (DIC), placental abruption or uterine rupture may occur [8]. Our hospital is one of the referral centers for complicated deliveries. First, we aimed to determine the maternal outcomes and complications in women with stillbirth. Then, the risk factors for stillbirth were evaluated via prepartum circumstances, delivery complications, operative obstacles, and postpartum processes in this study.

Materials and methods

This retrospective study was conducted at a high-volume university-affiliated research and training hospital between June 2016 and June 2020. It was approved by the Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences Ethics Committee with the decision number 2011-KAEK-25 2020/03-14 in 4th of March 2020. The Declaration of Helsinki guidelines were followed.

The deliveries during the study period were evaluated and data were collected from the hospital registry and the patients' hospital files. The study population was divided into two groups as those giving stillbirth and live birth (control).

Patients with multiple pregnancies and comorbid diseases were excluded from the study. Patients' characteristics, birth weight, hospital stay, and delivery type were examined. Concomitant diseases in pregnancy such as PE, gestational diabetes mellitus (GDM), fetal anomaly and PPRM, and the complications such as uterine atony, abruptio placenta, postpartum hemorrhage (PPH), DIC and uterine rupture were assessed from the patients' files, hospital registry and operation notes. Women who experienced uterine atony, abruptio placenta, DIC, interventions for PPH such as B-Lynch suture, Bacri Balloon Tamponade, hypogastric artery ligation, re-operation, hysterectomy, uterine rupture, bladder injury, intraabdominal hemorrhage, and need for blood product transfusion were included in a group titled "Severe Obstetric Complication." Patients who experienced febrile morbidity, endometritis, retained placenta, the need for blood product transfusion in the post-partum period, wound infection or dehiscence, thromboembolic events, need for reoperation, and maternal death were enrolled in a group titled "Postpartum Complication". The sociodemographic characteristics and delivery outcomes of patients were compared between the two groups.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Armonk, NY, USA). Shapiro Wilk test was performed to evaluate whether the variables were distributed normally. Non-normally distributed continuous variables were expressed as median (minimum-maximum), while categorical variables were presented as frequency and percentages. Mann Whitney U test was used to compare non-normally distributed continuous variables between two groups while Chi-square or Fisher's exact test was performed for categorical variables. Multivariate logistic regression analysis was used to predict risk factors for stillbirth. A *P*-value < 0.05 was considered statistically significant.

Results

A total of 46019 births occurred during the study period. The number of stillbirths was 520, with a rate of 11.2:1000 births. Obstetric outcomes and maternal complications were increased, maternal age was significantly higher ($P < 0.001$), hospital stay was longer ($P < 0.001$) and birth weight were lower ($P < 0.001$) in the stillbirth group. Moreover, the women in stillbirth group experienced more adverse perinatal complications such as fetal anomaly ($P < 0.001$), PPRM ($P < 0.001$), PE ($P < 0.001$), GDM ($P < 0.001$), abruptio placenta ($P < 0.001$), uterine rupture ($P < 0.001$), uterine atony ($P < 0.001$), PPH ($P < 0.001$) and DIC ($P < 0.001$). The rates of severe obstetric and postpartum complications were 14.2% and 12.1%, respectively in the stillbirth group, both significantly higher than the livebirth group ($P < 0.001$).

Individual investigation of severe obstetric complications revealed that hysterectomy was performed in six patients. Two of them were re-operated due to massive hemorrhage, and two patients underwent hysterectomy due to placenta accreta spectrum. Two patients were admitted to the adult intensive care unit due to massive bleeding and massive blood product transfusion.

No significant difference was found between stillbirth and control groups in terms of delivery type, baby gender, and the presence of placenta previa. The sociodemographic characteristics and perinatal features of the study population were presented in Table 1.

Estimated risks of stillbirth associated with risk factors were calculated by logistic regression analysis and demonstrated in Table 2. Compared with the control group, patients with fetal anomaly, GDM and abruptio placenta had a 3.1-fold (OR 3.170; 95% CI 1.592-6.315, $P < 0.001$), 15.2-fold (OR 15.203; 95% CI 8.368-27.621, $P < 0.001$) and 18.221-fold (OR 18.221; 95% CI 9.121-36.402, $P < 0.001$) increased risk of stillbirth, respectively.

Table 1: The sociodemographic characteristics and perinatal features of the study population

	Stillbirth (n=520)	Live Birth (n= 6521)	P-value
Age (years)	28 (14-45)	24 (13-44)	<0.001 ^a
Race (n, %)			<0.001 ^b
• Turkish	358 (68.8%)	3933 (60.3%)	
• Foreign	162 (31.2%)	2588 (39.7%)	
Delivery Type (n, %)			0.313 ^b
• Vaginal	330 (63.5%)	4281 (65.6%)	
• Cesarean	190 (36.5%)	2240 (34.4%)	
Hospital Stay (day)	3 (1-25)	2 (1-20)	<0.001 ^a
Baby gender (n, %)			0.06 ^b
• Male	286 (55%)	3303 (50.7%)	
• Female	234 (45%)	3218 (49.3%)	
Birth weight (gram)	1402 (500-5300)	3200 (500-5350)	<0.001 ^a
Birth weight (n, %)			<0.001 ^b
• >4000g	10 (1.9%)	287 (4.4%)	
• 2500-4000g	108 (20.8%)	5733 (88%)	
• 2500-1500g	125 (24%)	412 (6.3%)	
• 1500-1000g	103 (19.8%)	41 (0.6%)	
• 1000-500g	174 (33.5%)	48 (0.7%)	
Fetal Anomaly (n, %)	48 (9.2%)	27 (0.4%)	<0.001 ^b
PPROM (n, %)	16 (3.1%)	46 (0.7%)	<0.001 ^b
Preeclampsia (n, %)	41 (7.9%)	93 (1.4%)	<0.001 ^b
GDM (n, %)	36 (6.9%)	73 (1.1%)	<0.001 ^b
Abruptio placentae (n, %)	64 (12.3%)	24 (0.4%)	<0.001 ^b
Placenta previa (n, %)	5 (1%)	26 (0.4%)	0.06 ^b
Uterine Rupture (n, %)	4 (0.8%)	6 (0.1%)	0.001 ^b
Uterine Atony (n, %)	11 (2.1%)	13 (0.2%)	<0.001 ^c
PPH (n, %)	24 (4.6%)	58 (0.9%)	<0.001 ^b
DIC (n, %)	40 (7.7%)	24 (0.4%)	<0.001 ^b
Severe Obstetric Complications (n, %)	76 (14.6%)	188 (2.9%)	<0.001 ^b
Postpartum Complications (n, %)	63 (12.1%)	143 (2.2%)	<0.001 ^b

a: Mann-Whitney U test, b: Chi-square test, c: Fisher's exact test, DIC: Disseminated intravascular coagulopathy, GDM: Gestational diabetes mellitus, PPH: Postpartum hemorrhage, PPRM: preterm premature rupture of membranes

Table 2: Multivariate logistic regression analysis to predict risk factors for stillbirth

	P-value	Odds ratio	95% CI for Exp(B)	
			Lower	Upper
Age	<0.001	1.001	0.883	0.922
Race	0.931	0.988	0.752	1.298
Birth weight	<0.001	1.002	1.002	1.002
Fetal anomaly	0.001	3.170	1.592	6.315
PPROM	0.082	0.370	0.150	0.917
Preeclampsia	0.078	0.478	0.260	0.881
GDM	<0.001	15.203	8.368	27.621
Abruptio placenta	<0.001	18.221	9.121	36.402
Uterine Rupture	0.588	1.740	0.234	12.921

GDM: Gestational diabetes, PPRM: preterm premature rupture of membranes

Discussion

Stillbirth is the disastrous end of pregnancy. Despite the economic costs for the countries and the governments, the psychological consequences are tremendous for the families [9]. Almost 98% of the cases occur in low and middle-income countries, and one of the reasons for these high rates is difficulty of access to health care. The Millennium Development Goal has declared to decrease the stillbirth rates below 12 per 1000 births in all countries by 2030 [10]. Most of the developed countries have already reached that target nonetheless, approximately 23600 stillbirths occurred annually in America and the rates hardly decreased during the last decade [5]. The stillbirth rate of our hospital was 11.2 per 1000 births, which can be considered a

success due to the millennium target. Our rates might be higher than those in the peripheral centers because of being a referral center in that region. Contemporary studies have reviewed the possible reasons for stillbirth. Evaluation of the stillbirth was suggested in terms of detailed medical and obstetric history, an autopsy of the baby, placental pathology, genetic evaluation, Lupus, feto-maternal hemorrhage diseases, infections, inherited thrombophilia, endocrinologic diseases [11,12]. Despite these all investigations, most stillbirths remained unexplained.

The purpose of the study was to determine the characteristics of the patients and the maternal outcomes of women who experienced stillbirth. These women were older than the controls however, the median age of the patients was 28 years. The rate of women ≥ 35 years old was 22%. Recent studies also reported that advanced age was related to stillbirth; however, it was not easy to determine the proper threshold age for stillbirth [13,14]. The quality of the oocytes diminishes with age, which might be the reason for the increment of stillbirth, along with the adverse maternal and neonatal outcomes. Birth weight was lower in the stillbirth group. The rates of the babies <1000gr and <1500 gr were 33% and 53% respectively. These rates were also crucial because the stillbirth rates tend to decline in the third trimester in America however, the rate remained stable in women who experienced stillbirth within the second trimester [15]. In almost 10% of the women in the stillbirth group, the babies had fetal anomalies. It was obvious that congenital anomalies were one of the main reasons of stillbirth [16], yet the reason for the high rate was that the women in our country did not accept termination of the pregnancy even if the anomaly was incompatible with life, due to cultural beliefs. Approximately 40% of the patients who gave birth in our hospital were Syrian immigrants. Ethnicity was thought as a cause in increasing stillbirth, such as the non-Hispanic black race [12]. Comparison of the groups in terms of race was significantly different; however, we did not find any significant differences between the Turkish and Arabic women in multivariate logistic regression analysis.

Delivery type of women who gave stillbirth and live birth did not differ significantly. Obstetric conditions such as abruptio placenta, placenta previa totalis, fetal presentation, cephalopelvic examination, and history of uterine scar were the main determinants of the management. Some authors depicted that the labor would start spontaneously within 1-2 weeks after the death of the fetus, yet we did not consider expectant management in any of our patients [11, 17]. Women were at risk of coagulopathy abnormalities unless the delivery occurred within 3-4 weeks after fetal demise [8,18]. Forty patients experienced DIC with a rate of 7.7% in this study. One of the reasons for the high rate of DIC could be related to the high number of patients with abruptio placenta and preeclampsia. Although the benefit of serial laboratory tests for DIC has not been exposed properly, between admitting the patient and the delivery, we obtain serial laboratory tests like fibrinogen, complete blood parameters, and prothrombin time daily.

We use misoprostol, dinoprostone, or oxytocin to initiate or augment uterine contractions. For women without history of uterine scar, 200-400 micrograms of misoprostol was administered every 4-8 hours interval via the vaginal or

sublingual route in the second trimester. An intra-amniotic balloon was used on the second day of the labor induction. Approximately 50 to 80 cc of saline solution was infiltrated into the balloon. Half dose of misoprostol was used in women with earlier uterine scars. Use of dinoprostone, misoprostol (with a dose of 25-50 microgram via vaginal or oral route every 4 hours) are recommended in patients without cesarean history. Oxytocin could be administered in women with or without earlier uterine scars in the 3rd trimester of gestation. We do not recommend prostaglandins for women with uterine scar history. Repeat cesarean operation is also preferable in these patients. Maternal wish for the delivery type is essential.

Considering that all adverse maternal outcomes, such as uterine atony, PPH, DIC, postpartum complications, and obstetric complications, were more frequent in the stillbirth group, expectant management was not appropriate for our clinic. All these complications differed significantly in stillbirth patients. Studies in the literature revealed that women with stillbirth had an increased risk of serious adverse maternal outcomes [19-22]. These complications occurred during the postpartum period, thus, early intervention such as utilizing uterotonic agent after the delivery, and reserving blood products before delivery might decrease their rate.

The factors increasing the risk of stillbirth were age, birth weight, fetal anomaly, GDM, and abruptio placenta. Preeclampsia was assumed as one of the biggest risk factors for stillbirth [2,22,23]. Women with stillbirth experienced preeclampsia more than the control group; however, the multivariate logistic regression analysis revealed that preeclampsia did not increase the risk of stillbirth. That could be related to the close follow up in prenatal care. Almost all women diagnosed with preeclampsia were hospitalized and utilized adequate treatment at our hospital. During hospital stay, these patients were informed about fetal well-being and obstetric emergencies. PPRM might be a risk factor for stillbirth, yet it was not always possible to distinguish whether the rupture of membranes was the reason or the result of stillbirth. Gestational diabetes mellitus and abruptio placenta increased stillbirth rate with the odds ratios 15 and 18, respectively. It was well known that pre-existing diabetes was associated with stillbirth and adverse maternal outcomes [7, 24]. Contemporary studies determined that GDM was related to stillbirth, similar to our study [6, 25]. Even the pathophysiology of the relationship between GDM and stillbirth could not be enlightened properly, the undoubted fact is that the glycemic control of the patients with GDM or preexisting diabetes would protect fetuses from mortality. Our study revealed that abruptio placenta was the most crucial cause of stillbirth, like those in the literature. Abruptio placenta not only causes stillbirth but also maternal adverse outcomes such as uterine atony, peripartum hysterectomy, and DIC, especially in delayed cases [8,17,26,27]. Approximately half of the placenta abruptio cases could not be detected by ultrasound, especially acute abruptio [28]. We perform immediate delivery in the suspicion of placenta abruptio by clinical findings or ultrasonographic evaluation. Women with stillbirth had longer hospitalization periods. It is well known that pregnancy is a disease that predisposes to thrombosis. Prolonged hospital stay and immobility are the major risk factors for

thrombosis. Patients should be encouraged to mobilize and utilization of low molecular weight heparin is essential to prevent embolism [29].

One of the aims of this study was to evaluate severe complications. Seventy-six patients (14.6%) experienced severe complications including hysterectomy, re-operation, blood product transfusion, and need for intensive care unit admission, which revealed that stillbirths should be delivered in fully equipped hospitals when possible.

Limitations

Despite its single-center nature, the number of patients included in each study group was high. Its retrospective design was a limitation, and we could not obtain the anthropometric parameters of the patients.

Conclusion

Stillbirth is a disaster for families. Delayed intervention could also cause serious maternal adverse outcomes. Abruptio placenta and GDM were the main risk factors for stillbirth. GDM screening and adequate glycemic control might protect the fetuses. Emergent delivery in abruptio placenta is crucial. The type of delivery should be tailored individually based on obstetric history, gestational week, and fetal conditions. To avoid embolism, mobilization and low molecular weight heparin should be administered.

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