Antepartum İntrauterin Fetal Ölüm ile ilişkili Risk Faktörleri

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ÖZET:

Amaç: *Zeynep Kamil Hastanesi doğum kliniğinde intrauterin fetal ölüm nedeniyle yatan hastaların oranını, neden olabilecek etyolojik faktörleri, bu hastalara yapılan klinik yaklaşımı, riskli gebelikleri belirlemek ve sağlıklı anne ve yenidoğan oranını arttırmak için gerekli önlemleri önceden tahmin etmek amaçlanmıştır.*

Gereç ve Yöntem: *Ocak 2006- Ocak 2009 tarihleri arasında kliniğimizde intrauterin fetal ölüm nedeniyle yatmış 514 hastanın dosyaları incelenmiştir. 22-42. haftalar arasında doğum yapmış hastalar çalışmaya dahil edilmiştir. Bu hastaların 40 da istek üzerine bebeklerine otopsi yapılmıştır. Antepartum tekil, ölü doğum yapan bu hasta grubu, grup 1 olarak kabul edilirken, 153 tekil, sağlıklı doğumla sonuçlanan hasta grubu, grup 2 olarak kabul edilmiştir.*

Bulgular: *Antepartum ölü doğum oranı %1.2 olarak bulunmuştur. Ortalama doğum haftası ve ortalama bebek doğum ağırlığı 1. grubta istatiksel olarak anlamlı düzeyde düşük saptanırken, yatıştaki ortalama sistolik, diastolik kan basıncı, maternal hipertansiyon, maternal sistemik hastalık, intrauterin gelişme geriliği ve anhidroamnios görülme oranı 1. grubta istatiksel olarak anlamlı düzeyde yüksek bulunmuştur($p<0.01$). En sık antenatal ölüm nedeni olarak %67,7 oranında açıklanamıyan nedenler bulunurken, bunu sırasıyla preeklampsi (15,8%), plasenta dekolmanı (7,4%), konjenital anomaliler (5,3%), maternal diyabet (2,1%) ve Rh izo-immünizasyonu (1,8%) takip etmiştir. Yapılan perinatal otopsilerin %45'de fetal ölüm nedeni olarak konjenital anomali saptanırken, 2,5%'da fetal enfeksiyon, 52,5%'da fetal anoksi saptanmıştır.*

Sonuç: *İntrauterin ölü doğumların ideal bir şekilde değerlendirilmesi tartışmalıdır ve çeşitli medikal faktörler bunu etkiler. Çalışmamızda ölü doğumların %67,7 açıklanamıyan nedenler oluşturuken, en yaygın ikinci neden ise preeklampsi olarak saptanmıştır (%17,2). Doğumdan sonra antifosfolipid sendromu, herediter trombofililer, konjenital enfeksionların araştırılması ve otopsi yaptırılması ölü doğumların nedenlerini belirlemede yardımcı olabilir.*

Anahtar Kelimeler: *İntrauterin fetal ölüm, etyoloji, risk faktörler*

ABSTRACT:

Risk Factors associated with antepartum Intrauterine Fetal Death

Objective: *To investigate the frequency, etiology, management of intrauterine fetal death and to determine risk of pregnancies and to predict necessary precautions to provide increased healthy maternal and newborn rate.*

Material and Methods: *From January 2006-January 2009, a total of 514 fetal deaths were identified through the Zeynep Kamil Gynecologic and Pediatric Training and Research Hospital registries of labor units. The principal criteria of selecting variables intrauterine fetal death between 22-42 weeks of gestation. In this period, 40 fetal deaths referred for autopsy. The patients had intrauterine fetal deaths were accepted as group 1. 153 singletons live born were randomly selected as a control group in the same population and accepted as group 2.*

Results: *In this study, intrauterine fetal death rate was 1.2% in 3 years in group 1 gestational age, median birth weight was significantly lower than group 2 ($p: 0.001$). Systolic and diastolic blood pressure at diagnosis, maternal hypertension, maternal systemic disease, intrauterine growth restriction rate and anhydramniosis in group 1 was significantly higher than group 2 ($p<0.01$). The most common causes of intrauterine fetal deaths were unexplained with a rate 67.7%. The other determined causes of intrauterine fetal deaths were preeclampsia (15, 8%), placental abruption (7.4%), congenital anomalies (5.3%, maternal diabetes (2.1%), RH Isoimmunization (1.8%), respectively. The results of the perinatal autopsy; 45% of the fetal deaths caused by congenital anomalies, 2.5% of the fetal death associated with infection and 52.5% of the fetal deaths ascribed to anoxia were found.*

Conclusion: *The optimal evaluation of intrauterine fetal death is controversial and is influenced by several medical factors. In our study 67.7% of the fetal death cases were classified as unexplained, second most common reason was preeclampsia (17.2%). Testing for antiphospholipid syndrome and hereditary trombophilias, congenital infections and autopsy after delivery may help to define potential causes of intrauterine fetal death.*

Key Words: *Intrauterine fetal death, etiology, risk factors*

INTRODUCTION

Stillbirth is defined as intrauterine fetal death at 20 weeks of gestation or later, infants with a birth weight 500 g or higher born showing no signs of life (1). Rate of intrauterine fetal death is 5 per 1000 singleton births. Over the past decade, perinatal mortality rate significantly reduced but intrauterine fetal death rate did not decline as rapidly as neonatal death rate. Especially in developing countries perinatal mortality rate is high, many of these deaths are intrauterine fetal deaths (2). Certain causes of fetal death, including syphilis, Rh immunization, preeclampsia, and diabetes, have shown significant declines over the past several decades. However, many losses continue to occur from intrauterine infections, lethal malformations, fetal growth retardation, and ablatio placenta (3). Despite the efforts to identify the etiologic factors contributing to fetal death, in many cases it is difficult to find the certain etiology of intrauterine fetal deaths. A significant portion of fetal deaths are still classified as unexplained intrauterine fetal demise. This proportion of unexplained deaths in all intrauterine fetal death is between 12% and 67% in literature (4, 5, 6,). Maternal blood tests like Toxoplasmosis, Cytomegalovirus, Herpes Simplex Virus, antinuclear antibody(ANA), antiphospholipid antibody and lupus anticoagulant, fetal autopsy and chromosomal analysis may help to investigate possible causes of unexplained ante partum fetal deaths (6,7,8). The death of a fetus in utero for any reason is a tragedy, defining a specific cause makes easy to physiological adaptation. Despite this fact relatively little attention has been focused on intrauterine fetal death during the past decades. This study was conducted to investigate the frequency, etiology, management of intrauterine fetal death and to determine risk of pregnancies and to predict necessary precautions to provide increased healthy maternal and newborn rate.

MATERIALS AND METHODS

This case controlled retrospective study was carried out in Zeynep Kamil Gynecologic and Pediatric Training and Research Hospital, Istanbul. Among 43.042 births in the period from January 2006-January 2009, a total of 514 fetal deaths were identified through the hospital registries of labor units. The principal criteria of selecting variables were intrauterine fetal death (the death of a fetus prior to onset of labor) between 22-42 weeks of gestation. In this period, 40 fetal deaths referred for autopsy. All information about cases was obtained from computer records and patient files. The patients had intrauterine fetal death were accepted as group 1. 153 singletons live born were randomly selected as a control group in the same population and accepted as group 2. Intrauterine fetal death was diagnosed by antenatal real time ultrasound examinations and fetal anomalies were detected by antenatal ultrasound and postnatal physical examination and autopsy.

We included all women were diagnosed as singleton intrauterine fetal death after 22 weeks of gestational age with fetal weight 500 g or higher. Women with previous uterine surgery or uterine anomaly, embryo reduction, multiple pregnancies and inadequate clinical information were excluded from the study. Gestational age was calculated from the routinely used ultrasound examination in early pregnancy. In the only case where no ultrasound was performed in early pregnancy, gestational age was determined from the menstrual history. Factors that were considered to be associated with intrauterine fetal death included maternal age, parity, history of abortion, numbers of previous fetal death, systemic and diastolic blood pressures, hematocrit levels, maternal systemic diseases, preeclampsia, placental abruption, RH Isoimmunization, maternal diabetes, amniotic fluid volume, fetal anomalies were evaluated. Data were analyzed using NCSS 2007&PASS 2008 Statistical Software (Utah, USA). These 2 groups were compared using chi-square test, student t test and Mann Whitney U test where applicable. Stepwise logistic regression analyses were performed for multivariate analysis. A $p<0.05$ in any test was considered significant. Results were evaluated in 95% confidence interval.

RESULTS

During the study period we examined 514 patients who presented with singleton intrauterine fetal death at a median gestational age of 30 weeks. The total number of births were 43042 and intrauterine fetal death rate was found 1, 2% in this period. A total of 40 (6%) of women with intrauterine fetal death consented to perinatal autopsy. The demographic and clinical characteristics of these women are shown in **Table 1**.

Table 1: The demographic and clinical characteristics of pregnancy

	Study Group mean±SD	Control Group mean±SD	^p
Age	27.37±6.10	27.88±5.13	NS
Gravidity	1.05±1.63	2.27±1.51	NS
Parity	1.05±1.21	0.99±1.15	NS
History of abortion	0.35±0.74	0.24±0.63	NS
Previous history intrauterine fetal death	17(3.3%)	5(3.3%)	NS
Maternal hypertension			
Yes	196(38.2%)	32(20.9%)	**0.001**
No	317(61.8	121(79.1%)	
Maternal systemic disease			
Yes	19(3.7)	0	**0.016**
No	495(96.3%)	153(100%)	
Intrauterine growth restriction			
Yes	66(12.8%)	3(2.0%)	**0.001**
No	448(87.2%)	150(98.0%)	
Preeclampsia			
Yes	103(20.0%)	23(15.0%)	NS
No	411(80.0%)	130(85.0%)	
Gestational age	30.16±4.90	36.95±2.65	**0.001**
Systolic Blood Pressure at diagnosis	121.94±20.97	116.67±16.78	**0.003**
Diastolic Blood Pressure at diagnosis	80.53±14.18	73.66±11.79	**0.001**
Hemoconcentration			
Yes	78(15.2%)	22(14.4%)	NS
No	436(84.8%)	131(85.6%)	
Anhydramniosis			
Yes	69(13.4%)	0(0.0%)	**0.001**
No	445(86.6%)	153(100%)	
Oligohydramniosis			
Yes	78(15.2%)	15(9.8%)	NS
No	436(84.8%)	138(90.2%)	
Polyhydramniosis			
Yes	22(4.3%)	7(4.6%)	NS
No	492(95.7%)	146(95.4%)	
Birth wieght	1695.8±962.082	3147.75±647.87	**0.001**
Fetal gender			
Female	248(48.2%)	80(52.3%)	

^ Student t test ^^ Mann-Whitney test…….+ Ki kare test

There is no statistical difference in terms mean maternal age, gravidity, parity, history of abortion, history of the previous intrauterine fetal death, preeclampsia, oligohydramniosis, polyhydramniosis, malpresentation, hemo-concentration, fetal gender between group 1 and group 2 (p>0.05). In group 1 gestational age, median birth weight was significantly lower than group 2 (p: 0.001). Systolic and diastolic blood pressure at diagnosis, maternal hypertension, maternal systemic disease, intrauterine growth restriction rate and anhydramniosis in group 1 was significantly higher than group 2 (p<0.01). Intrauterine mortality risk was increased in preeclampsia but seems to have a little impact (odds ratio [OR] 1.42, 95% confidence interval [CI] 0.86-2.32). When using logistics regression analysis intrauterine growth restriction rate was significantly higher in study group (p: 0.001, OR 7.36, 95%CI 2.28-23.77) in **Table 2**.

Table 2: Logistic regression analysis for multiple variables

	B	S.E	Sig.(p)	Exp(B)	95.0% CI for EXP(B) Lower	Upper
IUGR(1)	2.01	0.61	0.00	7.45	2.26	24.54
ht(1)	0.93	0.23	0.00	2.52	1.60	3.97

Variable(s) entered on step 1:preeclampsia, IUGR, maternal hypertension (ht), maternal systemic deseases

As indicated in **table 3**, the most common causes of intrauterine fetal death were those categorized as ‘‘unexplained’’, with a rate 67.7% (348). The other determined causes of intrauterine fetal death were preeclampsia (15, 8%), placental abruption (7.4%), congenital anomalies (5.3%), maternal diabetes (2.1%), RH Isoimmunization (1.8%), respectively. Preeclampsia with placental abruption was seen in 15 of 514 women in the study group. When the perinatal autopsy was analyzed, the cause of death for each 40 fetuses was indicated in **Table 4**.

Table3: The most common causes of stillbirth

	N(514)	%
Unexplained	348	67.7
Preeclampsia	81	15.8
placental abruption	38	7.4
congenital anomalies	27	5.3
maternal diabetes	11	2.0
RH Isoimmunization	9	1.8
Preeclampsia with placental abruption	15	2.9

Table 4: Vaginal examination results and labor parameters and induction types of patients

	Study group mean±SD (mean)	Control group mean±SD (mean)	p
#Effacement (%)	39.20±33.32	42.42±29.02	0.239
#Dilatation (mm)	20.85±4.52	20.61±2.24	0.183
Baseline vaginal examination			
<70-80 %and <30mm	339(66%)	101%(66)	0.989
?70-80% and 30-40mm	175(34%)	52(34%)	
#Latent labor duration(hour)	11.86±10.06	7.11±8.86	**0.001**
#Total length of labor(hour)	17.78±20.36	9.65±13.14	**0.001**
Misoprostol			
Yes	182(35.4%)	1(0.7%)	**0.001**
No	332(64.6%)	152(99.3%)	
Oxytocin Induction			
Yes	300(58.4%)	50(32.7%)	**0.001**
No	214(41.6%)	103(67.3%)	

+ Ki-kare test # Mann-Whitney test

18 (45%) of the fetal deaths caused by congenital anomalies, 1(2.5%) of the fetal death associated with infection and 21(52.5%) of the fetal death ascribed to anoxia were found. Central nervous system (CNS) anomalies (15%) were found to be the most common anomaly in cases were referred to fetal autopsy in **Table5**.

Table 5: Characteristics of Labor

		Study group n(%)	Control group n(%)	+p
Presentation	Head	425(82.7)	143(93.5)	**0.006**
	Breech	68(13.2%)	10(6.5%)	
	Foot	12(2.3%)	0(0.0%)	
	Transverse	9(1.8%)	0(0.0%)	
Mode of delivery	NSD	413(80.4%)	78(51.0%)	**0.001**
	Cesarian	101(19.6%)	75(49.0%)	
Episiotomy	Yes	106(25.7%)	60(77.0%)	**0.001**
	No	307(74.3%)	18(23.%)	

We evaluated the digital vaginal examination baseline results and labor parameters and induction types of patients in **Table 6**.

Table 6: Causes of death in fetal autopsy

Cause of death	n	%
Congenital anomaly	18	45
Infection	1	2.5
Anoxia	21	52.5

There were no significant difference in baseline vaginal examination of patients, interval from baseline cervical effacement to complete effacement, interval from baseline cervical dilatation to complete dilatation between 2 groups (p>0.05). Women in study group had longer median duration of latent labor (p: 0.001) and total length of labor (p: 0.001). In study group misoprostol treatment rate and required oxytocin induction was significantly higher than control group (p: 0.001). Malpresentation, especially breech presentation rate was significantly higher in study group (13.2% vs. 6.5%; p: 0.01). In our study vaginal delivery rate was significantly higher and episiotomy rate was significantly lower in study group (p: 0.001; p: 0.001) **(Table 7)**.

Table 7: Congenital anomalies referred to fetal autopsy in study group

	n	%
CNS/Neural tube defects	6	15
Heart defects	5	12.5
Kidney defects	4	10
Abdominal wall defects	2	5
Hydrops fetalis	1	2.5

Postoperative complication rate and boom curettage rate was significantly higher in study group (8.8% vs. 0.7%; and 6.4% vs. 0.0%; p: 0.001). Blood transfusion rates of two groups was not significantly different (p>0.05).

DISCUSSION

In our study, intrauterine fetal death rate was 1.2% in 3 years and 142 (27.6%) cases were multiparous women. As a different; Kale et al. (9) reported that intrauterine fetal death rate was 4.1%i n 4 years, this rate was higher than literature. There are several causes of intrauterine fetal death, may be classified to maternal, fetal and placental reasons (10). Maternal factors include age, pregnancy history, blood type, Rh status and genetic load. Results of several studies are controversial. Some studies reported that maternal age was an independent risk factor (11, 12), some reported that maternal age did not affect intrauterine fetal death rate in pregnant women. (13). In our study, the mean maternal age was 27 in both study and control group and there was no statistically significant difference. Although it is not known why advanced maternal age is an independent risk factor for fetal death, older women are more likely to have multiple gestations, fetal chromosomal abnormalities, hypertension and gestational diabetes, all of which are risk factors for fetal demise (14). The fact that women with a previous intrauterine fetal death are at increased risk of intrauterine fetal death in future pregnancies is well known (15). In our study previous intrauterine fetal death history was not different between two groups. In addition, Froen et al.(16) reported that there was nine-fold risk of intrauterine fetal death in maternal hemoconcentration (hemoglobin>13 g/dl). We did not find significant difference in hemoconcentration levels between groups.

In literature, 25- 40% of intrauterine fetal death are due to fetal causes (10). Fretts et al. (17) reported that 35- 40% of intrauterine fetal deaths were due to fetal causes include congenital anomalies, infections, malnutrition, nonimmune hydrops and anti-D isoimmunization. In our study fetal causes was found 7, 1 %, lower than literature. This might

be due to deficient information about fetal infection from our patient files and lower incidence of autopsy rate. Rh immunization (1, 8%) and congenital anomaly (5, 3%) were the most common fetal causes of intrauterine fetal death in our study. We found also, the mean birth weight of intrauterine fetal death cases (1695 g) was significantly lower than control group (3147 g). Huang et al. (19) reported that fetal death rate was increased (OR: 2, 8) when fetal birth weight was between 2, 4 and 10 percentiles. The incidence of intrauterine fetal death caused by fetal infections remains constant. Several studies reported that 5, 6% of intrauterine fetal death were caused by chorioamnionitis and fetal or intrauterine sepsis (17, 20- 23). Bernirschke et al. (6) documented that fetal congenital infections were the main factor in intrauterine fetal death. In our study, when autopsy to examine, the incidence of infection was found 2, 5%. The other fetal cause related to intrauterine fetal death is congenital anomalies. Central nervous system are the most common causes of congenital anomalies that cause intrauterine fetal death (24, 25). Pauli et al. (20) reported that fetal congenital anomalies were presented in majority of the intrauterine fetal death cases. However Copper et al. (21) reported that 5, 6% of intrauterine fetal deaths were related with prenatally diagnosed congenital anomalies. As as similar, we found congenital anomaly rate was 5, 3% and CNS anomalies were found to be the most common congenital anomalies referred to fetal autopsy. Likewise Özkan et al.(27) reported that congenital anomalies was the most common diagnosis in 362 cases of fetal autopsy between 1992 and 2005, CNS anomalies were found to be the most common anomaly in these cases too. A complete autopsy with histology should be performed and should include accurate measurements to aid in assessing gestational age to define etiologies, risk factors associated with intrauterine fetal death(3). In our study there were 40 cases of fetal autopsy, there was no significant difference between fetal gender, 18(45%) of the 40 the fetal deaths caused by congenital anomalies, 1(2, 5%) of the cases had association with infection and 21(52, 5%) other cases were ascribed to anoxia. Unexplained ante partum intrauterine fetal death rate is 12-67% (4, 5). Some studies reported that with proper fetal autopsy and laboratory tests, and with careful investigation of antenatal history some centers had been able to determine a cause in 90% of cases (28). Huang et al. (19) reported that 27% of ante partum intrauterine fetal deaths were unexplained and most of them occurred later than 35 weeks of gestational age. Several studies in literature found that unexplained fetal death was observed more than 50% of fetal deaths, these results correlate with our findings (5, 29). We could criticize that the reason of higher unexplained fetal death in our study was due to the retrospective investigation and improper referral to fetal autopsy and deficient information about fetal infection. IUGR is an important risk factor of intrauterine unexplained fetal death. Froen et al. (16) reported that IUGR is the most important risk factor for sudden intrauterine unexplained fetal death (OR: 7, 0), 52% of cases were related to IUGR. In our study IUGR rate in study group (12, 8%) was significantly higher than control group (2%). Relative risk for fetal death in IUGR was 7, 36. Abruptio placenta is also related to intrauterine fetal death and is the leading factor in placental reasons. Abruptio placenta is seen with maternal hypertension in half of the cases (30). Several studies documented that abruptio placenta were found 12- 16% of the intrauterine fetal death cases (9, 10, 12, 31). In our study abruptio placenta (7, 4%) was the third most common reason of fetal death, preeclampsia with placental abruption was seen in 2, 9% women in study group.

Hypertension and diabetes are two of the most common medical disorders to complicate pregnancy. Population based studies showed a two-fold to four fold risk of intrauterine fetal death in women with diabetes (32, 33). However with optimum preconceptional care and management, the risk of perinatal death is only marginally raised above that of the general population (34). Gürel et al. (35) repotted that, preeclampsia and eclampsia were seen in 18, 6% of the intrauterine fetal death cases and the risk was increased in pregnancies complicated with HELLP syndrome. In our study 15, 8% of the cases had preeclampsia, 1, 6% of the cases had chronic hypertension, 2, 1% of the cases had diabetes.

The optimal evaluation of intrauterine fetal death is controversial and is influenced by several medical factors. In our study 67, 7% of the fetal death cases were classified as unexplained, second most common reason was preeclampsia (17, 2%). Maternal hypertension and carbohydrate intolerance related fetal deaths could be reduced by proper preconceptional and antenatal care. Testing for antiphospholipid syndrome and hereditary trombophilias, congenital infections may help to define potential causes of intrauterine fetal death. Also, after delivery consent should be sought for autopsy. Autopsy can determine and/or confirm numerous other cases of intrauterine fetal death and help to guide future pregnancy management, in addition to the identification of birth defects and morphologic abnormalities suggesting genetic or developmental anomalies. Our intrauterine fetal death rate was higher than our national perinatal mortality rate. This reason might be due to deficient antenatal medical care in primary and secondary medical centers and because of our hospital is an important reference center in our country. Intrauterine fetal death rate can be decreased by increasing antenatal care services in primary and secondary centers, detecting high risky pregnancies in earlier gestational weeks and taking required medical precautions. Previous fetal death history or birth of an infant with congenital anomaly remains an important risk factor in subsequent pregnancy and should be investigated in antenatal visits.

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