

A comparison of the etiology of early versus late fetal death from a single center



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ABSTRACT

Fetal death is one of the most devastating complications in obstetrics which remained understudied in our population. This study was done to study the maternal and fetal risk factors that lead to fetal death. To compare the rate of different etiologies in early versus late Fetal Death (FD) in cases of FD presented to King Khalid University Hospital, Riyadh, Saudi Arabia. A retrospective cohort study was conducted from 2006-2013 and cases were classified into Early FD (20-33 weeks + 6 days) and late FD (≥ 34 weeks) groups. A total of 26539 births including 304 cases (1.14%) of FD occurred during the study period. About 24 cases were excluded from the final analyses due to missing records or incorrect coding. The remaining 280 subjects were categorized into early (46.4%) and late (53.6%) IUGR groups. A substantial number of subjects from early (46%) and late (68%) FD groups did not have regular antenatal care. There were no significant differences in the etiology of FD such as obstetric complications, maternal medical diseases, fetal congenital anomalies, umbilical cord abnormalities, and maternal/fetal infections between the two groups. Intrauterine growth restriction (IUGR) and Gestational Diabetes Mellitus (GDM) were significantly associated with late IUGR (41 vs. 18.4% and 20.7 vs. 7.7%, respectively). Placental abnormalities were higher in the late FD group, although the difference was not statistically significant. Fetal death isn't a rare incidence. IUGR and GDM are significantly associated with increased frequency of late IUGR. Further research is needed for a firm understanding of the incidence of IUGR in Saudi Arabia.

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1. Introduction

Fetal Death (FD) is one of the most devastating obstetric complications with international estimate of 2.6 million cases annually (Cousens et al., 2011). The American Congress of Obstetrics and Gynecology defines fetal demise as a fetal death that occurs during pregnancy at ≥ 20 weeks' of gestation (ACOG, 2009) although different countries and organizations consider a range from as early as 16 weeks up to 28 weeks. Surprisingly, this subject is understudied, either due to the small proportion of cases that undergo a full post mortem examination (Amir et al., 2009) or because the reasons for FD in 25-60% of the cases are unexplained (The Stillbirth

Collaborative Research Network Writing Group, 2011; Huang et al., 2000; Frøen et al., 2001; Yudkin et al., 1987).

Interestingly, the current scientific evidences indicate that most cases of FDs could be preventable, although further research on the possible etiologic factors is needed in order to develop better preventive strategies in the near future (Lawn et al., 2011; McClure et al., 2006; Stanton et al., 2006).

The current study aims to investigate the possible etiologies of the reported cases of FD in our center and compare the rate of different etiologies in early versus late FD.

2. Materials and methods

A retrospective cohort study of all cases of FD that occurred or are presented to King Khalid University Hospital between 2006 and 2013 was conducted. The study was approved by the institutional ethics review board. Hospital information system was used to identify all cases of

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FD or stillbirths during the specified time period. The charts of identified cases were then manually checked to confirm their eligibility, which is based on antenatal ultrasound findings of absent fetal cardiac activity and confirmed by Apgar Score of 0 at birth. Total number of births during the study period was 26,539 births including 304 cases (1.14%) of IUFD. Twenty-four cases were excluded from analysis due to missing records or incorrect coding, leaving 280 cases (92.1%) as the cohort for analyses. The cases were divided into two groups: Group 1 - FD between 20 - 33 weeks and 6 days of gestation (N=130) and Group 2 - FD > 34 weeks of gestation (N=150).

The collected data included: maternal age, gestational age at presentation, body mass index (BMI), presence of antenatal care during the specified pregnancy, parity, mode of delivery, previous history of Fetal Death, maternal medical problems, maternal blood type and Rhesus (Rh) status, history of antepartum hemorrhage, premature rupture of membrane, history of intrauterine growth restriction, gestational diabetes mellitus, preeclampsia, umbilical cord knots, history of antenatal infections. In addition, fetal gender, birth weight, ultrasound reports for any anomalies were retrieved. Placental histopathology reports were reviewed for the following features: infarctions, chorioamnitis, hemorrhage, calcifications, knots, funitis, intervillous fibrin deposition, chorangiosis, and placental weight. Placentas and umbilical cords were examined for macroscopic and microscopic variations. Data was

analyzed using SPSS (Statistical Product and Service Solutions) software using Chi-square and Student t-test for analyses. A p value <0.05 was considered as statistically significant.

3. Results

A total of 280 early and late FDs were reported in this study. The mean maternal age and parity for women from both groups was comparable, however, gestational age ($p=0.0001$) and BMI ($p=0.002$) were significantly higher in women who experienced late IUFD (Table 1). About 40.7% of women in the early FD group and 32% in the late IUFD group did not have a regular antenatal care. In early FD, 98 women (75%) had normal vaginal delivery, 22 (17%) had assisted breech delivery, and 10 women (8%) underwent cesarean section. For women in late FD group, 118 cases (79%) had a normal vaginal delivery, 15 cases (10%) had assisted breech vaginal delivery, and 17 cases (11%) had cesarean section. There was no significant difference based on gender of fetus between the two groups (50.1% female fetuses and 49.9% male in group of early IUFD vs 57% female and 43% male fetal deaths in late FD group. Two cases in group 1 and 6 cases in group 2 had multifetal pregnancies. A comparison of the etiological factors that in early and late IUFD was performed (Table 2). The proportion of subjects with gestational diabetes ($p=0.002$) and intrauterine growth restriction ($p=0.000$) was significantly increased in subjects from the late IUFD group.

Table 1: The basic characteristics of the two groups

	Early FD (n=130)	Late IUFD (n=150)	P value
Maternal age Mean \pm SD	29.6 \pm 7.4	30.8 \pm 7.6	0.183
Gestational age Mean \pm SD	28.4 \pm 3.3	37.4 \pm 2.1	0.0001
Parity Mean \pm SD	2.4 \pm 2.8	2.3 \pm 2.5	0.753
BMI Mean \pm SD	29.8 \pm 5	31.9 \pm 6.3	0.002

Moreover, the proportion of subjects with hypothyroidism, umbilical cord knots and polyhydramnios was relatively higher in the late IUFD group. Interestingly however, a substantial number of subjects from early IUFD group showed a previous history of IUFD, preterm premature rupture of membranes, RH-ve status, antepartum hemorrhage, placental abruption and

oligohydramnios (Table 2). With regards to antenatal infections, there were no documented positive cultures in either groups. No cases of toxoplasmosis were found. However, Hepatitis B positivity was found in 4 cases in late IUFD group and rubella infection was reported in eight and 14 cases in early and late IUFD groups, respectively.

Table 2: Rate of etiological factors in early and late IUFD groups

	Early IUFD (n=130)	Late IUFD (n=150)	P value
Pre-existing DM	8 (6.2%)	10 (6.7%)	0.861
Chronic hypertension	3 (2.3%)	4 (2.7%)	0.848
Hypothyroidism	6 (4.6%)	11 (7.3%)	0.342
Gestational diabetes mellitus	10 (7.7%)	31 (20.7%)	0.002
Previous history of IUFD	17 (13.1%)	13 (8.7%)	0.234
Preeclampsia	4 (3.1%)	5 (3.3%)	0.903
Preterm Premature rupture of membranes	11 (8.5%)	6 (4%)	0.119
RH -ve	13 (10%)	7 (4.7%)	0.084
Umbilical cord knots	1 (0.8%)	5 (3.3%)	0.139
Intrauterine growth restriction	23 (18.4%)	59 (41%)	0.000
Antepartum hemorrhage	19 (14.6%)	13 (8.7%)	0.119
Placenta abruption	14 (10%)	11 (7.3%)	0.427
Oligohydramnios	3 (2.3%)	0 (0%)	0.133
Polyhydramnios	2 (1.5%)	7 (4.7%)	0.133

Microscopically, abnormal placental findings were found to be high in both groups with 55.6% of

histopathology reports in group 1 and 60% in group 2 showing positive findings. Placental abnormalities

in both groups are detailed in [Table 3](#). While a higher proportion of subjects from late IUFD group experienced chorioamnitis, calcifications, knots, and chorioangiomas, the early IUFD group predominantly showed hemorrhage, funitis and intervillous fibrin

deposition. However, these abnormalities were not significantly different in both groups. Although a good number didn't show any abnormalities, some placentas had 3 or more abnormalities.

Table 3: Placental microscopic findings

	Early FD (n=130)	Late IUFD (n=150)	P value
Infarction	42 (33.9%)	45 (34.6%)	0.899
Chorioamnitis	12 (9.7%)	18 (13.8%)	0.303
Hemorrhage	12 (9.7%)	6 (4.6%)	0.116
Calcifications	2 (1.6%)	6 (4.6%)	0.170
Knots	1 (0.8%)	3 (2.3%)	0.336
Funitis	7 (5.6%)	2 (1.5%)	0.076
Intervillous fibrin deposition	25 (20.2%)	21 (16.2%)	0.407
Chorioangiomas	4 (3.2%)	6 (4.6%)	0.569

4. Discussion

The current study was undertaken to understand the etiologies and risk factors associated with FD in early versus late gestational ages. To the best of our knowledge, there is a lack of literature that reported the incidence of FD in Saudi Arabia. An incidence of 1.14% (95% C.I: 1.01%- 1.27%) was reported from our center suggesting a much higher estimate than developed countries such as USA (0.625%) and UK ([The Stillbirth Collaborative Research Network Writing Group, 2011](#); [CEMACH, 2005](#)).

Current literature shows that several risk factors are associated with FD. The most commonly reported factors are nulliparity, maternal medical diseases, cholestasis of pregnancy, smoking, obesity, low educational attainment, previous compromised obstetric history and advanced maternal age ([Flenady et al., 2011](#)). The existing body of evidence shows variable etiological factors of FD. The incidence of such factors differs according to the populations and gestational age of the pregnancies. The most common reported causes are preeclampsia, infection, congenital or karyotypic anomalies, placental problems associated with growth restriction ([The Stillbirth Collaborative Research Network Writing Group, 2011](#); [Silver et al., 2007](#); [Lawn et al., 2005](#)).

It is well known that advanced maternal age is as an independent risk factor for FD, even after adjusting for other risk factors ([Dodds et al., 2003](#); [Jacobsson et al., 2004](#); [Mutz-Dehbalae et al., 2014](#)). Although the mean age of our study subjects did not exceed more than 30 years and there was no statistically significant difference between the early versus late FD with regards to maternal age, around 30% mothers were ≥ 35 years. In addition, obese pregnant women were more likely to have FD compared to lean women ([Stephansson et al., 2001](#); [Cedergren, 2004](#)). About 53.2% of our FD cases were obese and the BMI of subjects in the late gestational age group was significantly higher compared to the early group ($P=0.002$). Such finding is probably explained by the fact that obese women may be less able to perceive decreased fetal movements and that they are more likely to develop gestational diabetes, gestational hypertension and preeclampsia ([Stone et al., 1994](#); [Maasilta et al., 2001](#)).

Diabetic mothers were reported to have a higher risk of FD in several well-conducted studies. A relative risk of 4.56 ($P < 0.0001$) with no difference in the prevalence between type 1 and type 2 diabetes ([Tennant et al., 2014](#)) and a 2-3 folds higher chance of IUFD than the general population ([Cundy et al., 2000](#)). About 6.42% of the IUFD cases in our study had pre-existing diabetes mellitus – although there was no statistical significant difference between the early versus late FD groups. The smaller number of diabetic mothers in this study could have influenced the study results. On the other hand, data pertaining to the influence of gestational diabetes (GDM) on IUFD are controversial with research depicting no role or an increased risk ([Silver et al., 2007](#); [Dudley, 2007](#)). However, our study results suggest a significant role of GDM in FD. Furthermore, GDM prevalence was significantly higher in the late IUFD group (20.7% vs. 7.7%; $P = 0.002$) compared with early IUFD group. The biochemical mechanisms such as ketoacidosis, silent hyperglycemia and increased free radical production inherent to GDM could have played a role in causing IUFD ([Dudley, 2007](#)).

Another major risk factor for FD was IUGR which was observed in 29.3% of the FD cases in our study. Moreover, IUGR prevalence was significantly higher in the late versus early FD group (41% vs. 18.4%, p value 0.00). These results are in agreement with studies indicating that a significantly higher frequency of late FD in pregnancies are complicated by mild and severe fetal growth impairment compared to normal fetal growth ([Clausson et al., 2001](#)). Interestingly, a failure to properly diagnose and manage fetal growth restriction was the most common correctable error in cases of FD ([Kady and Gardosi, 2004](#)).

Placental pathology is considered as a major contributor to FD in several studies ([Amir et al., 2009](#); [The Stillbirth Collaborative Research Network Writing Group, 2011](#); [Aminu et al., 2014](#); [Korteweg et al., 2008](#)). A large retrospective cohort study by Amir et al. reported the common microscopic findings in placenta in pre-term vs term babies and those delivered before or after 34 weeks indicated histological evidence of uteroplacental insufficiency (one or more of the following: vascular occlusion, poor vascularity, intravascular thrombi and placental infarcts), cellular metaplasia and

histological evidence of chorioamnitis. Placental findings also indicated poor tissue vascularity and vascular occlusion in FD placentas delivered before 34 weeks, while placental bed infarcts were found more commonly in placentas delivered after 34 weeks. Some of these findings are also reported in our study. Although a high rate of pathological placental findings was reported in our study (58%), they were not significantly different in either of the gestational age groups. Many other etiological factors were associated with FD in our study including hypothyroidism, chronic hypertension, rhesus incompatibility, preterm premature rupture of membranes, previous history of FD preeclampsia and placental abruption – however, significance was not achieved between early vs late IUFD groups probably due to the relatively smaller number of patients.

The retrospective study design, inclusion of subjects from similar geographic and ethnic backgrounds and information from a single center could have influenced our study results by limiting the generalizability of our study results.

5. Conclusion

In conclusion, our study reported the frequency, etiologies and risk factors for IUFD in early and late gestational ages. Some of the significant risk factors and etiologies included gestational age and high BMI along with GDM and IUGR. In addition, many microscopic pathological findings were reported from the placenta of IUFD cases. The smaller population size and use of retrospective data from a single center limit the generalizability of our study results, although an overview estimate has been obtained. We therefore recommend additional studies with larger patient numbers from additional regions of Saudi Arabia including many centers to have a firm understanding of IUFD in Saudi Arabia. While fetal death continues to be one of the major traumatic events, further nationwide studies are not only required for an accurate estimation but also to put forward educational and awareness programs to limit the incidence of IUFD.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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