Intrauterine Fetal Death: A Review of 50 Cases in the City of Kashan- Iran, 2011-2012

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Abstract: Background: In one-third of the cases of intrauterine fetal death (IUFD) the cause is unknown; also, previous studies have not adequately determined the role of all possible factors. This paper reviews some of the factors contributing to the occurrence of IUFD. **Methods and Materials:** This was a case-control study approved by the institutional review board at Kashan University of Medical Sciences. All recorded 50 cases of IUFD during 2011-2012 in the city of Kashan-Iran were included in the study. Maternal and fetal data gathered included maternal age, gestational age, fetal sex, complete blood cells counts, renal function tests, level of blood glucose and viral infections. Data analysis was done using SPSS 14 software. **Results:** A significant correlation was found between family relation with husband and IUFD. Fetal sex was not an associated factor, though (P=.838). There was a significant association between maternal hemoglobin concentration, serum creatinin levels, and blood sugar with fetal death while Blood Urea Nitrogen (BUN) and Thyroid Stimulating Hormone (TSH) levels were not associated with the occurrence of IUFD. It was shown that the studied viral infections can increase the risk of IUFD (P=.012). **Conclusion:** This study found that the history of previous pregnancy loss, consanguinity and the viral infections are risk factors for IUFD. Maternal hemoglobin concentration, serum creatinin levels, and blood sugar were found to be important factors in IUFD while maternal age, fetal sex and the number of red blood cells were not confirmed in this study to be important factors.

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Introduction

The terms stillbirth and intrauterine fetal death both refer to the delivery of a fetus showing no signs of life such as heart beat or spontaneous respiration. The least gestational age defined for IUFD varies between 20 to 28 weeks. [4] More than 3.2 million stillbirths occur each year worldwide and it is considered to be one of the commonest and most important adverse outcomes of pregnancy. The incidence of IUFD is estimated to be 3 per 1000 pregnancies in developed countries and as high as 45 per 1000 pregnancies in developing countries. [1] Fetal death is a traumatic event and can be devastating for parents and clinicians. The causes of fetal death include: fetal causes (25-40%), placental causes (25-35%), maternal causes (5-10%) and in 25-35% of cases the cause remains unknown. [2-4] Determining the exact cause of IUFD can improve the mother's psychological adjustment; reduces the mother's feeling of guilt; determines the possible interventions to prevent its recurrence during subsequent pregnancies and provides useful information to other involved family members. As mentioned, in one-third of the cases of intrauterine fetal death (IUFD) the cause is unknown and previous studies have not adequately determined the role of all possible factors. Also it has been shown that the frequencies of the various etiologies of stillbirth differ among racial groups. With these in mind, we attempted to identify maternal and fetal factors involved in fetal deaths in our population in the city of Kashan.

Methods and Materials

This was a case-control study approved by the institutional review board at Kashan University of Medical Sciences. The study population consisted of 50 pregnancies which ended in stillbirth during 2011-2012 in hospitals affiliated to Kashan University of Medical Sciences. IUFD was defined as the fetal death at equal or more than 20 weeks of gestation and /or birth weight of equal or more than 500 grams. Ultrasonography was done, twice, by two different sonologists to confirm the diagnosis of the fetal death by documenting the absence of fetal cardiac activity. Then, an informed consent was obtained from the parents before entering in the study. The data for this case-control study was gathered using a standard questionnaire, which included the following: maternal age, gestational age (weeks), family relation with husband, history of previous fetal death, uterine and fetal abnormalities confirmed by ultrasonography. A specimen of 10 ml of the mother's venous blood was

drawn by a nurse; then, in order to keep the confidentiality of the participants, each specimen was tagged with a sample identification number, and was sent to the laboratory. The blood samples were checked for Complete Blood Count (CBC), Blood Urea Nitrogen (BUN), creatinin, blood glucose and Thyroid Stimulating Hormone (TSH) levels. After delivery, within maximum 12 hours of birth, 5ml of blood was taken from the umbilical vein. All samples were immediately transferred to -20 degrees Celsius; within 48 hours, blood samples were split into aliquots and were then stored at -70 C. Before Polymerase Chain Reaction (PCR) testing, frozen blood samples were thawed and then viral genome presence was studied by PCR endpoint assessment. In order to detect Cytomegalovirus (CMV) and Herpes simplex virus 1 and 2 (HSV1 and HSV2) the following PCR kits were used, respectively:

CMV/ 500 /800 IC end-point PCR kct |50 tests| Code V-7-50R

HSV 430/720 IC End-point PCR kct |100 tests| Code V-8-50R, manufactured by Sacace Biotechnologies.

Nogen Biotech Company's Parvo B19 PCR detection kit (cat #39500) was used for detection of Parvovirus B19. Isolation of genomic DNA was performed by using Amp DNA mini kit.

The control group subjects were chosen from the pregnant women with live fetuses referred to obstetrics clinics affiliated to Kashan University of Medical Sciences. In order to match the gestational age of the two groups, women with stillbirth were divided into 20-24 weeks, 25-28 weeks, 29-32 weeks, 32-36 weeks and more than 36 weeks. Then, 50 pregnancies with live fetuses and matching the same gestational ages were selected randomly using a random number table and the patients' files numbers. After obtaining the informed consent, the questionnaire was filled out and a specimen of 10 ml venous blood was taken and the samples were sent to the laboratory. The control subjects underwent abdominal ultrasonography all performed by one sonologist for placental localization and detecting uterine or fetal abnormalities.

The results were analyzed using SPSS software, version 14, for Windows. Descriptive analysis was done using Chi square, Independent T test, Fisher's Exact Test, Mann-Whitney U and Kolmogorov-Smirnov test. The results are expressed as mean value (standard deviation). A P value of less than.05 is considered significant.

Results

The mean value for gestational age was 27.6±5.69 in the case group and 27.52±5.9 in the control group (P=.945) and this shows that the two groups were well matched for the gestational age (Table 1). 48 stillborn babies (96%) were preterm (< 37 weeks gestation). Mean maternal age was 27.34±6.8 in the stillbirth group and 27.06±6.6 in live fetuses group and this difference was not statistically significant (P=.835). There was a statistically significant difference between the two groups regarding the history of miscarriage (P=.003) and it was found that women with a previous abortion had more than 5 times increased risk for IUFD (OR= 5.41, CI= 1.66-17.64). Consanguineous marriage was found to be a risk factor (P=.016) and considering the Odds Ratio of 3.45, it was found that in the presence of consanguinity, the increased risk is 3.5-fold (CI= 1.22-9.7). Fetal sex was not found to be a risk factor in our study (P=.683) (Table 2).

In order to study the distribution of the data, Kolmogorov-Smirnov test was performed and the means of the variables in the two groups were compared. The results of our analysis showed that the average concentration of hemoglobin in the two groups had a significant difference (P= <.001). There was no association between maternal BUN and TSH levels with stillbirth rate. The two groups were significantly different regarding maternal blood glucose and creatinin levels at admission (Table 3).

Studying the umbilical venous blood samples, no evidence of infections was found in the control group; in the stillbirth group, infection was identified in 6 cases (Parvovirus B19 [n=3], HSV1 [n=1], CMV [n=2]). So it is interpreted that being infected with one of the studied viruses is significantly associated with IUFD (P=.012) (Table5).

Discussion

In this case-control study, we tried to identify possible features associated with IUFD. Based on our analysis, it was found that women with a previous abortion had more than 5.4 times increased risk for IUFD. In their study of 112 women, Goy et al., found that a history of previous pregnancy loss was associated with a 1.98-fold increased risk of IUFD (CI=1.22-3.21). [1] There are also other studies which have shown an association of previous fetal demise with IUFD [2-4]. A study of 1050 women, done by Sharma et al., showed that women with a history of stillbirth had the highest risk of IUFD (OR=5.8, CI=3.7-9.0) [2]. However, Flenady [5] and Black [6] both believed that previous history of pregnancy loss does not increase the risk of subsequent stillbirths. We can justify concluding that this correlation between previous stillbirth and an increased risk of IUFD is due to maternal factors such as congenital or acquired uterine abnormalities, major untreated diseases or economical-social status.

As it was shown in our study, consanguinity between the parents can be a risk factor. In a study of

consanguineous marriage and pregnancy outcomes, performed in Oman by Mazharul Islam in 2013, it was confirmed that IUFD rate is significantly higher in consanguineous parents [7]. Similar results have been reported in other studies. [8, 9] However, some studies suggest controversial results that there is no association between family relation with husband and the risk of IUFD [10-12]. Consanguineous marriage is an important correlate of genetic problems, disorders of chromosomes and hereditary diseases that can lead to IUFD. However stillbirth is a complex variable to study and the exact association with an isolated factor such as family marriage is difficult to discern.

In this study, stillbirth was not associated with sex of the fetus. In the study of 100 subjects by Hossain et al. in Pakistan, IUFD was not significantly associated with fetal sex [13]. In one study of 672 cases of IUFD performed by Ingemarsson in Sweden, it was determined that the incidence of IUFD is similar in both sexes [14]. Contrary to these results, other studies have shown an association of male fetal sex with increased occurrence of IUFD. Patricia et al. suggested that male fetal sex is an independent risk factor for stillbirth and increases its incidence up to 1.5 times (OR= 1.5, CI=1.01-2.17) [15]. Hadar et al. also studied 105 cases of IUFD and found that there is an association with the male sex [16]. Sami et al. showed similar results [17]. Numerous previous studies have claimed that male fetal sex is a risk factor for adverse pregnancy outcomes such as gestational diabetes mellitus, placental abnormalities, disorders related to the cord and preterm labor [14 and 18-22]. These studies do not provide any demonstrable underlying cause for this association. The negative results in the current study may have resulted because of our small sample size or the different population genetic structure in our area. Further studies with larger population in different ethnic groups are needed to define the correlation between sex of the fetus and the risk of fetal demise.

In the current study, maternal hemoglobin concentrations in the stillbirth group were significantly lower than that of the live fetuses group. In a large study of 222164 pregnancies performed by Little et al. it was observed that maternal hemoglobin concentration was associated with IUFD and mothers in the stillbirth group had significantly lower hemoglobin levels compared to the controls [23]. Kidanto et al. compared anemic and non anemic pregnant women and reported that anemia significantly increases the risk of stillbirth and the risk increases with the severity of anemia [24]. Similar results are reported by Onadeko et al. [25]. In contrast to mentioned findings, in the study of 1354 cases of IUFD by Zhang et al. in China, IUFD was not associated with anemia and even it was claimed that lower hemoglobin levels tend to be protective [26]. Since the primary function of hemoglobin is to transport oxygen, reduced hemoglobin concentration leads to reduced maternal-fetal oxygen exchange so the fetuses of anemic mothers are more likely to suffer from antenatal hypoxia which can be lethal. On the other hand, an increased hemoglobin concentration accompanied by decreased plasma volume may increase the blood viscosity. Hyperviscosity of the maternal blood can disturb the blood flow into the intervillous space and impaired exchange of oxygen and nutrients may lead to fetal death. These two different mechanisms may explain contradictory results reported by different studies. Furthermore, these studies have been performed at different times during pregnancy and because of the different time frames it seems difficult to make comparisons between them. In order to be able to define the exact effect of maternal anemia on pregnancy outcomes, further studies should be conducted at similar time frames.

In our study, BUN and creatinin were checked as markers of kidney function and it was found that there is a correlation between serum creatinin and IUFD but no such association was found between BUN and stillbirth. Previous studies of the association between serum creatinin levels and pregnancy outcomes, have pointed out that in mild renal disease (serum creatinin <1.3 mg/dl) fetal loss rates is slightly higher than the control group [27-32]. In moderate renal disease (serum creatinin between 1.3-1.9 mg/dl) the probability of the fetal demise occurrence is markedly increased [31 and 33-38]. In severe renal disease defined as serum creatinin levels higher than 1.9 mg/dl it is usually difficult to evaluate the pregnancy outcomes due to low likelihood of conception and higher rates of early pregnancy failure among these women. But even if the pregnancy occurs, these women tend to have higher rates of fetal death than expected [37-41]. Consequently, considering the direct detrimental effects of the underlying renal disease on the growing fetus and the presence of the renal disease complications such as hypertension which predisposes poor maternal and fetal outcomes in this group, along with controlling the underlying renal disease, it is crucial to find a safe level of renal function with the least adverse fetal outcomes, by using indicators such as serum creatinin. This requires further studies.

We found that mothers in the IUFD group had higher blood glucose at admission and the difference between the two groups proved to be statistically significant. In their retrospective study of 4 million pregnant women, Melissa et al. showed that the risk of IUFD is significantly higher in diabetic mothers compared to non-diabetic ones. This increased risk was found in all studied age groups [42]. Faiz et al. believe that diabetes mellitus is an independent risk

factor for fetal death and it increases the risk of IUFD by 1.7 times [43]. Other studies, also, note the higher incidence of IUFD in diabetic women; Gardosi et al. reported a 3.9-fold increased risk of stillbirth in mothers with diabetes mellitus [44 and 45]. Hyperglycemia and diabetes damage blood vessels which can alter uteroplacental blood circulation; this, results in fetal hypoxia and acidosis which both predispose fetal death. Hypertrophic cardiomyopathy in infants of diabetic mothers which result from hyperglycemia can be another possible cause of death in these fetuses.

Our study did not show any significant association between TSH level and risk of fetal death. Other studies have suggested that a higher level of TSH even in the absence of overt hypothyroidism is a risk factor for IUFD [46 and 47]. Considering the fact that thyroid function tests are routinely screened as a part of our prenatal care, and thyroid disorders are usually corrected before initiation of pregnancy, the difference between our results and other studies may be explained.

In our study, a possible association was found between infections and stillbirth but this relationship was not confirmed with certain viral types. In a study of 62 cases of intrauterine fetal demise, Syridou et al. found that viral infections were significantly higher among the cases compared with the control group [48]. Embleton et al. reported that viral agents are the cause of 12.3% of IUFDs and in the study by Craven et al. it was noted that non identifiable viruses were the cause to more than 25-38% of stillbirths [50 and 51]. The role of intrauterine viral infections in fetal growth restriction, genetic abnormalities and fetal loss has been demonstrated in previous studies, but defining the commonest and the most important involved viruses requires well designed further studies of maternal and fetal histology.

Conclusion

In conclusion, based on the mentioned results, it is suggested that proper prenatal care including controlling diabetes mellitus, correcting maternal anemia, and screening for asymptomatic renal disorders be provided. Also, women with previous history of IUFD and a consanguineous marriage warrant careful assessment of fetal wellbeing and should be considered as high risk. Further histological studies of fetus are warranted to define the exact role of viruses in IUFD.

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