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UMBILICAL CORD THROMBOSIS: A METICULOUS CULPRIT OF INTRAUTERINE FETAL DEMISE

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ABSTRACT

Introduction: Intrauterine fetal demise (IUFD) is the most dramatic and often unpredictable pregnancy complication. Sixty percent of cases remain idiopathic despite numerous pathophysiological entities described in literature. The objective of this study was to identify potential risk factors and causes of IUFD. **Materials and Methods:** A retrospective, observational study conducted on pregnant women, who experienced a fetal loss at gestational age ≥ 24 weeks and birth weight ≥ 500 grams, at the Obstetric Discipline of Dr. I Cantacuzino Hospital. Data concerning demographics, maternal-associated pathology, delivery, fetal gender and birth weight, as well as autopsy findings were procured for the period between January 1, 2013 and December 31. Statistical analysis was carried out using GraphPad Prism with statistical significance set at $p<0.05$. **Results and Discussion:** Forty-three fetal losses were recorded in women ages 16-42 (average age 28.2 ± 6.4 years). Twelve mothers (27.9%) consented to fetal autopsy, which revealed the following causes of death: umbilical cord thrombosis (n=7, 63.9%), subchorionic thrombosis (n=2, 18.2%) and vasa praevia (n=2, 18.2%). Negative Docimasia tests placed time of death as antepartum in all autopsied fetuses. Cerebral hemorrhage was the most frequent autopsy finding (n=8, 72.7%). The following risk factors for umbilical cord thrombosis were identified: previous Caesarean Section ($p=0.0006$), lack of pregnancy monitoring ($p=0.0006$) and excessive gestational weight gain ($p=0.003$). **Conclusion:** Umbilical cord thrombosis is an increasingly frequent cause of spontaneous IUFD. Multicentric randomized controlled trials are needed to establish guidelines for anticoagulation in pregnancy. All pregnant women with abnormal coagulation parameters should be screened for thrombophilia.

KEYWORDS: intrauterine fetal demise, umbilical cord thrombosis, autopsy.

INTRODUCTION

Intrauterine fetal demise (IUFD) is the most dramatic and often unpredictable pregnancy complication. [1] Although a universal definition of IUFD is still lacking, the vast majority of professional medical societies consider spontaneous fetal loss at gestational age ≥ 24 weeks and fetal weight ≥ 500 grams. [2] In 2009, a staggering 3.3 million fetal deaths were recorded worldwide. The highest rate of IUFD was recorded in Pakistan (46.7 deaths/1000 live births) in contrast to the lowest rate noted in Finland (1.97 deaths/1000 live births). [3]

The pathophysiological mechanisms of IUFD are multifactorial comprising maternal, fetal and placental components.[1] The maternal component includes maternal-associated comorbidities, infection and trauma. Maternal-associated comorbidities such as gestational hypertension (GHTN), causing placental abruption), gestational diabetes, pre-eclampsia, antiphospholipid syndrome, thrombophilia and Rhesus isoimmunization have been demonstrated to be salient causes of IUFD. Infection refers to chorioamnionitis. Traumatic events pertain to blunt trauma, usually produced by falls resulting in uterine rupture.

Fetal causes encompass chromosomal anomalies resulting in malformations, intrauterine growth restriction (IUGR), and umbilical cord anomalies such as cord compression, velamentous insertion, true knotting and umbilical vessel thrombosis (TUV).

Placental pathology plays a fundamental role in the complex pathophysiological entities of IUFD. Placental

abruption and placental infarction secondary to postdate pregnancy are incriminating factors of IUFD. Despite the myriad of pathophysiological entities described in literature, [4] sixty percent of cases remain idiopathic.

The following are indicators of IUFD: absent fetal heart beats confirmed by two proficient ultrasonographists for a duration of three minutes, oligohydramnios, fetal hydrops and Spalding's sign (overlapping of fetal skull bones by collapse of the fetal brain). [5] Intrauterine fetal death is managed by induction, followed by vaginal delivery within twenty-four hours of diagnosis. In the case signs of sepsis are present, delivery by an emergency Caesarean Section is mandatory. When a fetus is retained for a period of three weeks, disseminated intravascular coagulation is imminent. [6] The objectives of this study were to identify potential risk factors and causes of IUFD.

MATERIALS AND METHODS

A retrospective, observational study conducted on pregnant women, who experienced a fetal loss at gestational age ≥ 24 weeks and birth weight ≥ 500 grams, from the Obstetric Discipline of Dr. I. Cantacuzino Clinical Hospital between January 1, 2013 and December 31, 2015. The inclusion criteria were gestational age ≥ 24 weeks, birth weight ≥ 500 grams and the period between January 1, 2013 and December 31, 2015. Pregnancy terminations were excluded from this study.

Data concerning the mother, fetus as well as maternal-fetal annexes was procured from patient records. Maternal data focused on demographics, maternal-associated pathology, level of education and method of delivery. The fetal parameters included gender and birth weight, as well as autopsy findings. Regarding maternal-fetal annexes, data from macroscopic and histopathological examinations were obtained from the Department of Anatomical Pathology. A database was created in Microsoft Excel 2010. Statistical analysis encompassed both descriptive and analytical tests and was carried out using GraphPad Prism with statistical significance set at $p < 0.05$.

RESULTS AND DISCUSSION

Forty-three fetal losses were recorded in forty-three pregnant women over a three-year period between January 1, 2013 and December 31, 2015. The age range of the pregnant women was between 16-42 years with an average age of 28.2 ± 6.4 years. The most frequent maternal age group was between 27-32 years (n=16, 37.2%) as depicted in **Figure 1**.

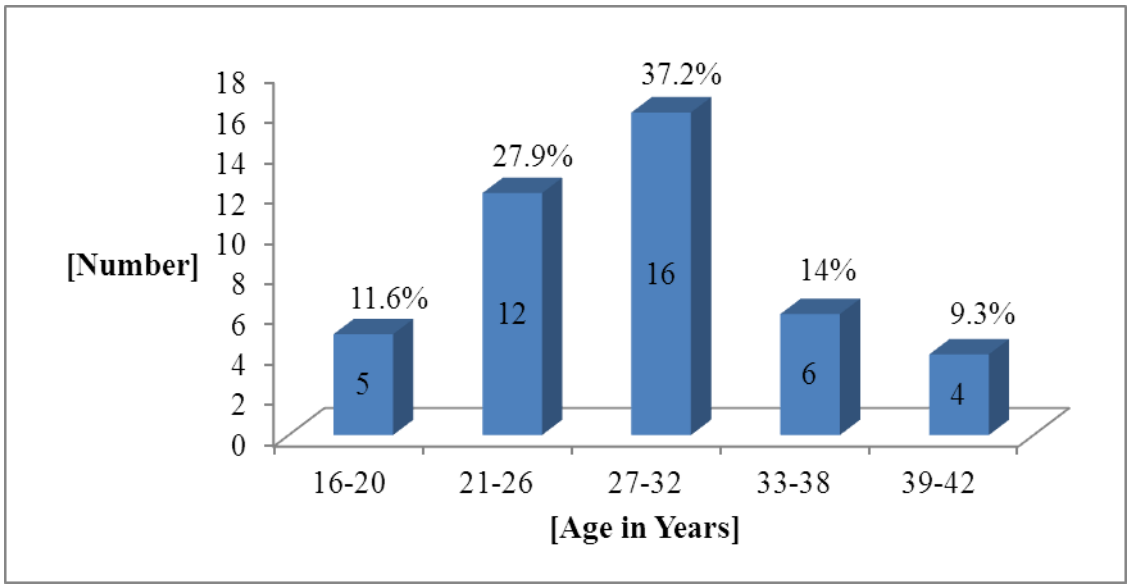

Figure 1: Distribution According to Maternal Age

Extremes of maternal age, defined as age ≤ 18 and ≥ 35 years were noted in nine women, comprising 20.9% of the study population. Two-thirds of the women were aged ≥ 35 years. Women were categorized according to parity as primipara (n=24, 51.8%), multipara (n=19, 44.2%) and grand multipara (defined as ≥ 5 deliveries) included in the multipara category (n=4, 21%). Gestational age ranged between 21-41 weeks with a mean of 32 weeks. A preponderance of third trimester pregnancies (n=38, 88.4%) was observed, compared to only 5 (11.6%) second trimester gestations.

Excessive weight gain in pregnancy was noted in the case of five (11.6%) women. Maternal educational level was stratified into primary school, secondary school and higher education. Eight women (18.6%) had a higher level of education. The chief complaints upon admission were abdomino-pelvic pain (n=27, 62.7%), painless vaginal bleeding (n=4, 9.4%) and painful uterine contractions (n=12, 27.9%). Maternal-associated comorbidities were present in nine women (20.9%), namely pre-eclampsia (n=4, 9.3%), Rhesus

isoimmunization (n=3, 6.3%) and one case each of GHTN (2.3%) and secondary anemia (2.3%).

Forty pregnancies were singleton (93%); all three multiple pregnancies were dichorionic, diamniotic twin pregnancies (n=3, 7%). All fetuses were either in longitudinal (n=39, 90.7%) or transverse lie (n=4, 9.3%). Eighty percent of the fetuses in longitudinal lie were cephalic presentations (n=37, 80.1%) compared to six breech presentations (13.9%). Nine women presented with ruptured membranes (20.9%). Amniotic fluid anomalies were noted in five women (11.6%), of whom three had oligoamnios (60%).

Pregnancy monitoring was lacking in twenty women (46.5%). Twenty-nine fetuses (67.4%) were declared dead upon admission of the mother to hospital. Fourteen fetuses died during maternal hospitalization (32.6%). The interval between admission and fetal death ranged between 1-5 days with an average of 2.5 ± 1.6 days. Vaginal delivery was the predominant method of delivery (n=23, 53.5%). Nine women (20.9%) had a scarred uterus secondary to one or more previous Caesarean Sections.

Twenty-three (53.5%) of the deceased fetuses were female. Fetal weight ranged between 500-3500 grams with an average weight of 1754.3 ± 819.5 grams, as demonstrated in **Figure 2**.

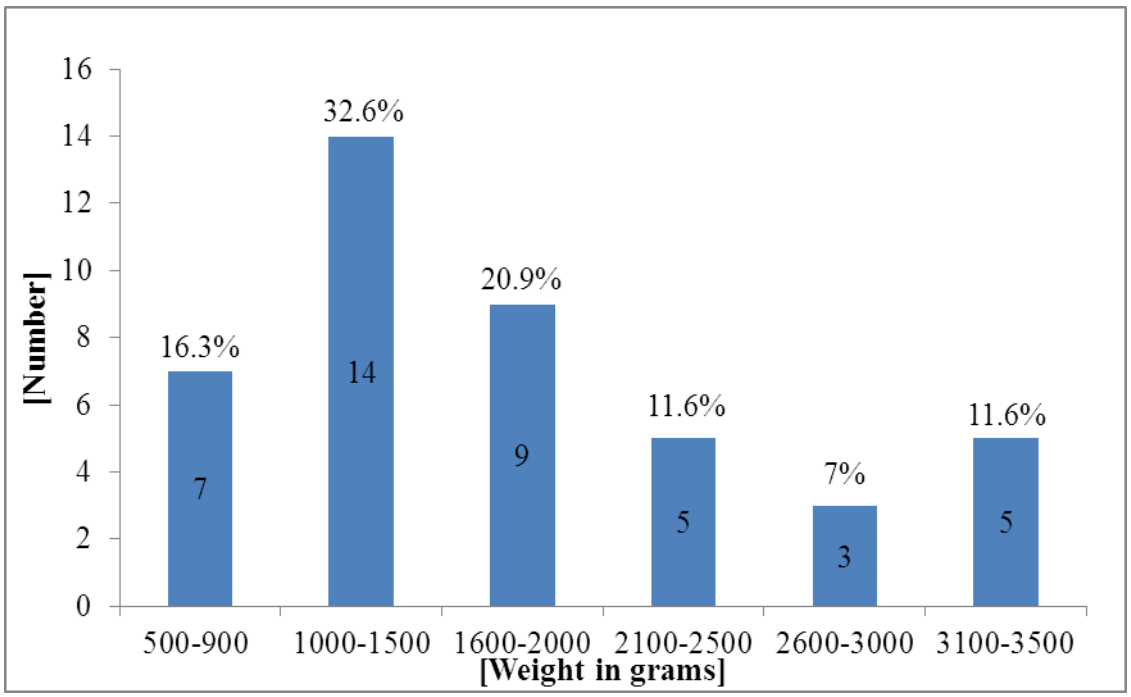

Figure 2: Fetal Weight

Intrauterine growth restriction (IUGR) was present in eleven pregnancies (22.6%). Eight fetuses were malformed (18.6%), of whom three (37.5%) presented multiple malformations. The single malformations (n=5, 45.5%) comprised anencephaly, varus equin, cheilopalatoschisis, Tetralogy of Fallot and atrial heterotaxy. The plurimalformations (n=3, 37.5%) consisted of Trisomy 18 (Edward's Syndrome), oro-facial-digitatal malformations and midline central nervous system anomaly with hydrocephalus.

Abnormal placentation in the form of placenta accreta and increta was present in two pregnancies (4.7%). Placental delivery was classified as spontaneous (n=29, 67.4%), assisted (n=13, 30.2%) and manual extraction (n=1, 2.3%). Sixteen placentae (37.2%) were deemed abnormal upon macroscopic examination, designated as edematous (n=7, 43.7%), microcalcified (n=3, 18.7%), infarcted (n=3, 18.7%) and meconium-impregnated (n=3, 18.7%).

Five cases of abnormal cord insertion were noted: marginal (n=2, 40%), velamentous (n=2, 40%) and furcate (n=1, 20%). Placental cultures were taken from all the placentae that were deemed abnormal upon macroscopic examination, yielding a diagnosis of chorioamnionitis in four cases (9.6%).

Twelve mothers (27.9%) consented to fetal autopsy. The cause of death (COD) was established in all autopsies: namely umbilical cord thrombosis (n=7, 63.9%), subchorionic thrombosis (n=2, 18.2%) and vasa praevia (n=2, 18.2%). Docimasia tests were performed on autopsied fetuses, all of which were negative, placing time of death (TOD) as antepartum. Hemorrhage was found in the following organs in descending order: brain (n=8, 72.7%), (p=0.33), lungs (n=6, 54.5%), (p=0.66), adrenal glands (n=6, 54.5%), (p=0.0001), kidneys (n=3, 27.3%), (p=0.03), heart (n=1, 9.1%), (p=0.0001) and liver (n=1, 9.1%), (p=0.0001), as shown in **Table 1**.

Table 1: Autopsy Findings by Organ

Organ examined	Normal	Hemorrhage	*p*-value
Brain	3	8	0.33
Lungs	5	6	0.66
Liver	10	1	0.0001
Heart	10	1	0.0001
Kidneys	8	3	0.03
Adrenal glands	5	6	0.66

Three fetuses exhibited autolysis (n=3, 27.3%). Desquamated fetal skin cells were found in six fetuses (54.5%), placing TOD as ≥ 72 hours. Histopathological examination of the umbilical cord revealed abnormalities in all cases: umbilical cord thrombosis (n=7, 63.6%), of which six (85.7%) were confined to the umbilical vein, hematoma (n=2, 18.2%) and edema (n=2, 18.2%).

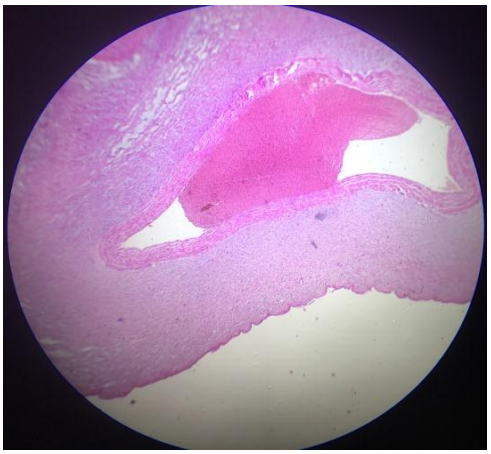

Figure 3: IUFD at 34 weeks gestation. Umbilical cord specimen. The umbilical vessels contain intraluminal partially degraded blood in a well-organized mass.

H&E, 10X

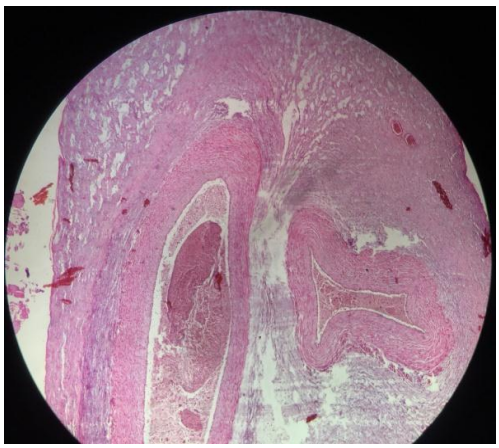

Figure 4: IUFD at 34 weeks gestation. Umbilical cord specimen. The umbilical vessels contain intraluminal partially degraded blood in a well-organized mass.

H&E, 4X

Histopathological examination of the placenta was undertaken in 38 cases (88.4%) and revealed necrosis (n=14, 36.8%), subchorionic thrombosis (n=7, 18.4%), microcalcifications (n=6, 15.8%), intervillous hemorrhage (n=4, 10.5%), edema (n=4, 10.5%) and infarction (n=3, 7.9%), as illustrated in **Figure 5**.

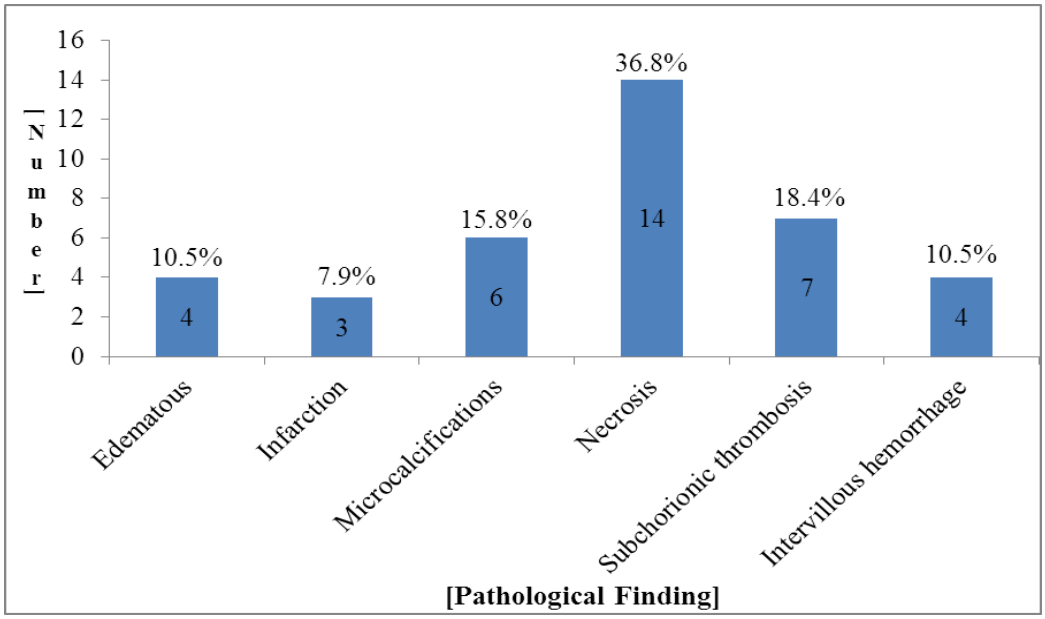

Figure 5: Histopathological Examination of the Placenta

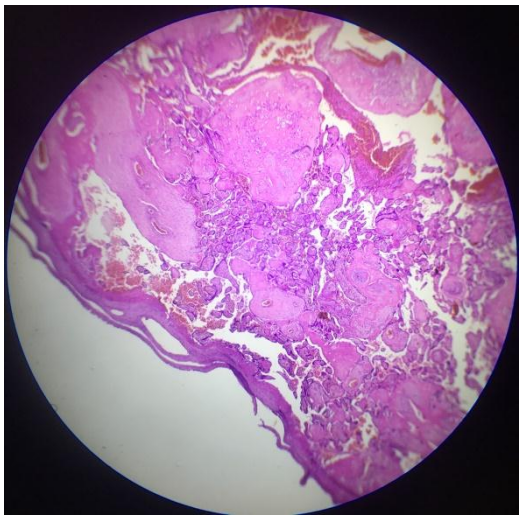

Figure 6: IUFD at 34 weeks gestation. Placental specimen featuring fibrinoid necrosis, hemorrhagic areas, microcalcifications and an acute inflammatory infiltrate.

H&E, 4X

Umbilical cord thrombosis was noted solely in the cases of IUFD occurring in the third trimester; range: 30-41 weeks, median 33 weeks. Thrombosis of umbilical vessels was established as the COD in fetuses whose mothers were aged 23-39 (average age 29.3 ± 5.9 years). All fetuses who died due to TUV were singletons in longitudinal lie, cephalic presentation.

Three mothers had comorbidities (42.6%), namely secondary anemia, GHTN and both pre-eclampsia as well as non-isoimmunized Rh incompatibility in one mother. None of the mothers exhibited an amniotic fluid abnormality prior to the death of their fetus. Four mothers (57.1%) delivered vaginally. Caesarean Section was performed in three mothers (42.9%), two of whom had a scarred uterus secondary to a previous Caesarean Section. Of the seven fetuses who died due to TUV, four (57.1%) were male.

Fetal weight ranged between 1500-3500 grams with an average weight of 2235.7 ± 676.2 grams. Intrauterine growth restriction was present in only one out of the seven fetuses with TUV (14.2%). Only one fetus (14.2%) was plurimalformed with Edward's Syndrome (Trisomy 18).

One case of placenta increta was encountered, mandating manual extraction. Of the total of five cases of abnormal cord insertion recorded in our study, only one abnormality (14.2%), namely velamentous insertion, was present in a fetus whose COD was established as TUV. One placenta (14.2%) from a mother whose fetus died secondary to TUV presented both chorioamnionitis and meconium impregnation.

The following risk factors for umbilical cord thrombosis were identified: previous Caesarean Section (p=0.0006), lack of pregnancy monitoring (p=0.0006) and excessive gestational weight gain (p=0.003).

Intrauterine fetal demise is one of the most scarcely studied obstetric complications, attributed mainly to a

low percentage of mothers who consent to fetal autopsy.[7]

Umbilical cord thrombosis, more clearly stated as thrombosis of the umbilical (TUV), has been clearly demonstrated to be associated with IUFD. [8-11] It is more frequently the culprit of late IUFD (after 28 weeks gestation), as was the case in our study (all cases ranged between 30-41 weeks gestation). [7] Thrombi have a predilection for the umbilical vein, [12] also a finding in our study (n=6, 85.7%). However, up to 15% of TUV cases have been shown to affect the umbilical artery alone. [10]

Avagliano et al. conducted a ten-year retrospective study of 317 consecutive fetal autopsies performed at a single center. From these 317 consecutive autopsies, 32 cases (10.1%) of TUV were identified, [13] compared to our study which identified 7 cases (16.9%) of TUV from 43 consecutive fetal autopsies. These figures demand a higher degree of attention be paid to TUV as a compelling cause of IUFD. Furthermore, the incidence of TUV as a cause of IUFD has been on the rise ever since the pioneering study performed by Heifetz in 1988. At that point in time, the incidence of TUV was 1/1000 in perinatal autopsies. [7] Subsequently, over the course of twenty-one years, the incidence of TUV among fetal autopsies reported by Avagliano et al. was an astoundingly 90 times higher in 2009 than in 1988. [12] Our study showed that female fetuses had a greater preponderance for TUV, in contradiction to other studies. [7] The mean maternal age in our study was 29.3 ± 5.9 years, lower than that reported by Avagliano et al.: 32.1 ± 5.1 years. [12]

To date, literature reveals a complete paucity of studies published regarding risk factors associated specifically with TUV. As such, we may only correlate our finding of Caesarean section as a risk factor for TUV (p=0.0006) with IUFD. Our finding of previous Caesarean Section (p=0.0006) as a risk factor for IUFD is consistent with a study conducted by Ohana et al. consisting of 1,694 IUFD cases between 1988-2009. [14]

In cases of undetermined IUFD after autopsy, histological examination of the placenta exhibited patterns of restricted umbilical blood flow, such as in the case of TUV. [15] Literature currently reveals a paucity of studies on risk factors associated specifically with TUV.

The placenta acts as an interphase between the maternal and fetal bloodstreams, thereby creating a complex biosystem. Anatomical analysis (both macroscopic and microscopic) of the placenta has shown to provide insight into circulatory disturbances of both maternal and fetal circulatory systems. Blood flow anomalies within the placenta are predominantly caused by TUV.[16] The etiopathogeny of thrombosis described by Virchow's triad encompasses hypercoagulability, endothelial damage and vascular stasis. [17] It is a well-known fact that pregnancy, itself, is a hypercoagulable state, although successful pregnancy outcome is highly dependent on the development of a low-resistance feto-maternal circulation. [18] Hypercoagulability has been shown to be associated with inherited and acquired thrombophilia, as well as maternal and fetal placental histologic anomalies. [19] A link between inherited maternal thrombophilia, especially homozygous Factor V Leiden, and fetal loss has been clearly demonstrated. [20] Interestingly, none of the women included in our study were diagnosed with thrombophilia. However, it is our belief that some of the women suffer from thrombophilia, although it is undiagnosed as a result of high costs involved with testing. Currently, guidelines regarding anticoagulation in pregnancy secondary to thrombophilia are still lacking and may warrant additional scientific efforts.

Despite gestational diabetes mellitus (GDM) being a well-established cause of IUFD in the third trimester, [21] to our surprise, none of the women in our cohort suffered from GDM.

The limitations of this study were a modest study sample, its retrospective nature and the fact that it was carried out in a single-center.

CONCLUSION

Thrombosis of umbilical vessels is an increasingly frequent cause of spontaneous IUFD that demands more attention in terms of prophylaxis and early management. To date, literature reveals a complete paucity of studies published regarding risk factors associated specifically with TUV. We present the following risk factors associated specifically with TUV: previous Caesarean Section (p=0.0006), lack of pregnancy monitoring (p=0.0006) and excessive weight gain in pregnancy (p=0.003).

Macroscopic and microscopic examination of the placenta is crucial in all cases of IUFD. The umbilical cord should be inspected for gross anomalies in terms of abnormal insertion in addition to microscopic examination for thrombi in its vessels in all cases of IUFD.

To further elucidate causes of IUFD, fetal autopsy should be performed on every case of IUFD. Physician counseling regarding the crucial role of fetal autopsy in determining the cause of death could be considered as a strategy to gain greater maternal consent for fetal autopsy. Fetal autopsy not only yields valuable information regarding maternal pathogenesis and the cause of fetal death, but also has a prognostic value that will aid family planning, as genetic anomalies may be detected.

Multicentric randomized controlled trials are needed to establish guidelines for anticoagulation in pregnancy secondary to thrombophilia. All pregnant women with

abnormal coagulation parameters should be screened for thrombophilia. Ultrasound screening of the umbilical vessel resistance and pulsatility index should be carried out earlier in pregnancy and followed up more diligently in the case of abnormal findings.

Performing studies focusing on identifying risk factors associated specifically with TUV is of paramount importance in decreasing the global burden of IUFD.

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