Unexplained Ten Consecutive Early Third Trimester Intrauterine Fetal Deaths: A Diagnostic Dilemma

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Citation

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Abstract

This report presents a case of unexplained ten consecutive early third trimester intrauterine fetal deaths in the absence of any maternal detectable risk factors and in presence of normal fetal growth. Detectable associations in tenth pregnancy were very low maternal serum alpha feto protein (<0.15 MOM MSAFP), turbid liquor amni and extensive placental pathology viz., fibrosis, hyalinization, infarction, narrowing as well as poor vascularization of chorionic vessels.

INTRODUCTION

Recurrent early third trimester fetal deaths may result from variety of causes like chronic maternal illness, Rh-isoimmunization, syphilis, uterine anomalies and chromosomal abnormality. Several reports also have indicated an association between recurrent fetal death with antiphospholipid antibodies[1,2,3], congenital protein C or protein S deficiency[4,5], activated protein C resistance[6], lupus anticoagulant[7], prothrombotic mutations[8] and disorders of maternal-placental interface, such as feto-maternal hemorrhage[9] as well as maternal floor infarction[10]. In some cases primary placetal pathology viz chorio-angiomas[11] of placenta, primary avascularity of placenta[12] and chronic villitis of unknown origin[13] has been implicated. However, universal acceptance of the later two associations are still lacking. We here report a case of ten consecutive early third trimester (27-31 weeks) fetal losses with very low maternal serum alpha feto protein (<0.15 MOM MSAFP), turbid liquor amni and extensive placental pathology viz., fibrosis, hyalinization, infarction, narrowing as well as poor vascularization of chorionic vessels.

CASE REPORT

A macerated stillborn female fetus was referred for fetal autopsy. The fetus was delivered at 31 weeks of gestation to para ten, hindu, brahmin, middle class mother who had noticed decreased fetal movements three weeks prior to delivery and loss of fetal movement 4-5 days before the delivery. The mother was 32 years and father 38 years old at the time of birth of the child. There was no history of consanguinity. The present pregnancy had remained uncomplicated untill decreased fetal movements were noticed around 27th week of pregnancy. At the onset of decrease in fetal movement an obstetric ultrasound was carried out privately that showed illsustained fetal breathing (at 27 weeks) and turbid liquor amni. All other fetal parameters were normal. Follow up ultrasound at the time of loss of fetal movement revealed fetal death at 30 weeks of gestation. Labour was induced by oxytocin infusion and a female fetus weighing 1.535 Kg was delivered vaginally. Autopsy findings revealed no intrauterine growth retardation (good subcutaneous fat and normal weight), no internal or external malformation & no umbilical cord pathology. However, thymus & placenta were hypoplastic and placenta was firm (nonspongy). Placental histopathology examination showed extensive placental fibrosis, hyalinization, infarction, narrowing as well as poorly vascularization of chorionic vessels (Fig.1 & 2).

Figure 1

Figure 1: (X50 magnification) and Figure 2: (X125 magnification). Section of placenta showing fibrosis, hyalinisation, poor vascularisation and narrowing of vessel lumen.

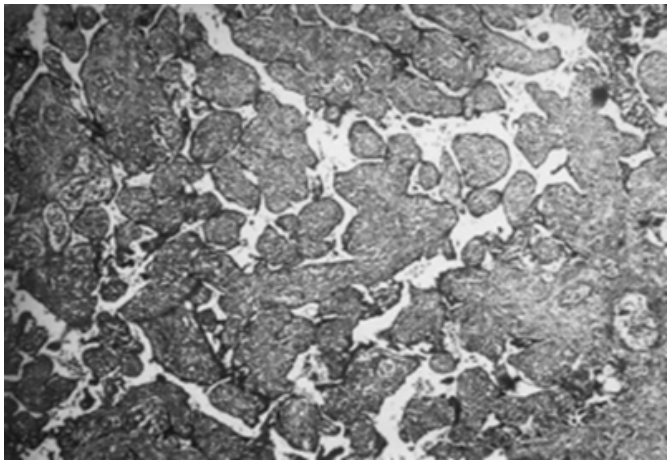
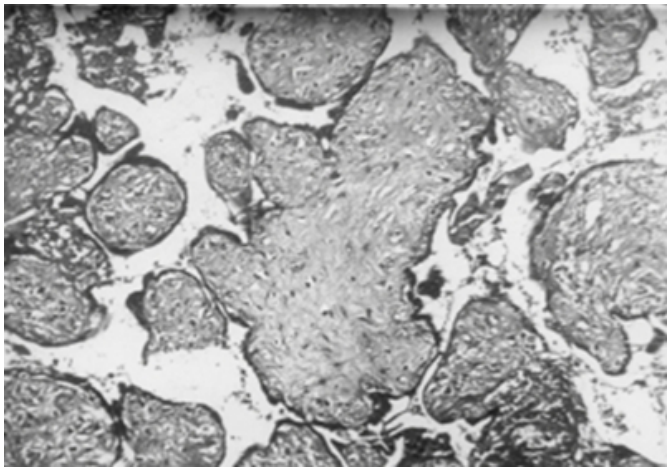


Figure 2



Similar autopsy findings were reported in previous pregnancy. Almost similar obstetrics history had followed in previous pregnancies. The mother was under care of private obstetricians throughout most pregnancies and fetal dath was unstoppable even after antiplatelet therapy in last pregnancy. All the fetuses were normal externally; seven were male and three were female. There were no signs of growth retardation in any of fetuses. The couple was investigated in detail in 10^{th} pregnancy and also in the interval period between 9^{th} & 10^{th} pregnancy. The findings are summarised in Table1. The mother was not known to have any chronic disease, however, she had two episodes of right sided hemiparesis at the age of 8 years and 14 years from which she had recovered fully.

Family history revealed no similar fetal losses. However, multiple sets of twin pregnancies were reported in first degree relatives of the couple (both sides).

DISCUSSION

Recurrent early third trimester fetal death may remain unexplained inspite of indepth investigation. The case which is described in this report is preferably termed as inadequately explained despite indepth investigations. As all her ten pregnancies ended in the same fashion and almost at the same period, we presume a common underlying etiopathologic factor. Our prime suspects are antiphospholipid like syndrome/antiphospholipid like syndrome and inherited thrombophilias (protein S deficiency, activated protein C resistance, prothrombotic mutations, etc). Primary antiphospholipid syndrome (APS) is unlikely in the absence of negative investigations (lupus anticoagnlant, platelet count, VDRL test, complements and anticardiolipin antibody). However, adverse pregnancy outcome has been reported in patients with APS with low positive autoantibody titre[14] as in our case. In addition Branch et al[15] earlier reported that some patients with this history may produce antiphosphatidylserine antibody. Similarly, Triplett et al[16] reported that patient with APS may have positive reaction only against phosphatidylserine or phosphatidylinositol. Although testing for anticardiolipin antibody may provide some insight into patient with APS, testing for phosphatidylserine antibody identifies some rare patient who are non-reactive for anticardiolipin and lupus anticoagulant[17]. Antiphospholipid like syndrome (in presence of absent autoantibodies)[18] could be the possibility for the underlying cause and is supported by the history of recurrent trainsient ischemic attack (in the form of hemiparesis), patern of recurrent fetal death after detection of fetal heart and placental histopathology viz. infarction, intravascular fibrin deposition and fibrosis[18]although placental changes could be partly due to post mortem changes. Placental fibrosis is commonly seen with macerated stillbirth (long standing intrauterine death). However, it is very unlikely that placental histologic changes are solely postmortem as indirect evidences (low MSAFP, turbid liquor amni, decrease fetal movement 2-3 week before fetal death and thymic hypoplasia) indicate its antenatal onset. Very low maternal alpha feto protein can be seen with chromosomal abnormality (trisomy 21, trisomy 18, 48,XXYY and triploidy)[19,20,21], placental chorioangiomas[11] or placental fibrosis. Very low MSAFP levels with later condition can be explained by lack of transfer of AFP from fetus to mother because of placental fibrosis and hypovascularity. The

reason for turbid liquor is not apparent. However, it was not due to oligohydramnios or amniotic infection or bleeding or meconium in amniotic fluid. Placental fibrosis and hypovascularity may probably the end result of chronic villitis of immunologic origin through antiphospholipid or antiphospholipid-like syndrome[18], activated protein C resistance[6], prothrombotic mutations[8] and anti-annexin V autoantibodies[22]. Placental fibrosis may also be seen with methyl parathion exposure[23,24], hyperthermia[25], hypoxia[26,27] and transforming growth factor-beta overactivity[26,28]. Chronic hypoxia is unlikely to be the underlying cause (commonly seen with pregnancy induced hypertension) as this results in minimal fibrosis of the villi, whereas a marked fibrosis with increase in stromal connective tissue and villous avascularity results from thrombosis in main stem and surface vessels[29] as seen with prothrombotic mutations[8] and antiphospholipid syndrome[18].

Possibilities like cogenital protein C deficiency, uterine anomalies, balanced chromosomal translocation in parents, etc were excluded by approporiate investigations (Table 1). Similarly, monogenic, polygenic, multifactorial, uniparental disomy and genomic imprinting as underlying cause is unlikely as none recurr in 100% offsprings. Maternal floor infarction or fetomaternal hemorrhage as cause is also unlikely in the absence of high MSAFP[30].

In conclusion we feel that evaluation of recurrent unexplained fetal death is incomplete unless it directs investigation towards detailed inmunologic (beyond anticardiolipin & lupus anticoagulant), inherited thrombophilias as well as placental pathology. Time has come to stress pathology of placenta as a factor in fetal demise and not only as part of epiphenomena.

Figure 3

Table 1: Summary of Investigations

Parameters	Results During Non-Pregnancy Interval	Results During 9th & 10th Pregnancy
Blood group & Type		
Wife	B +ve	B +ve
Husband	A +ve	Not done
Glucose tolerance test	Normal	Normal
Renal function test	Normal	Normal
TORCH Test	Negative	Negative
Listeria	No Growth	No Growth
α-Thallassemia Screening	Negative	Not done
Thyroid Function Test	Normal	Normal
Ultrasonography	**Normal uterus & adeneza**	**Turbid liquor after 24 weeks of pregnancy, No oligohydramnios**
Hysterosalpingography	Normal	Not Applicable
Chromosome Wife	46, XX (balanced translocation excluded by HRB)	
Chromosome Husband	46, XY (balanced translocation excluded by HRB)	
Platelets	Normal (2.2 lakh/ml)	Normal (2.8 lakh/ml)
VDRL	Non reactive	Non reactive
Lupus Anticoagulant	Normal	Normal
(Prothrombin time, Kaolin clotting time, activated partial thromboplastin time & dilute APTT)		
Anticardiolipin antibody		
IgM (N upto 10 EU)	14.2, 17.8	Not done
IgG (N upto 15 EU)	17.7, 21.5	15.5
Complement C3	68.88 mg/dl (WNL)	Not done
Complement C4	17.4 mg/dl (WNL)	Not done
Antinuclear antibody	Negative	Negative
Antimitockondrial Ab	Negative	Negative
Antismooth musle Ab	Negative	Negative
Anti dsDNA Ab	69.2 IU/ml (WNL)	63.9 IU/ml (WNL)
Anti paternal cytotoxic Ab	**Positive, 1:128 dilution**	**Positive, 1:128 dilution**
HLA Typing Wife	A1 A30 B7 B51 CW2 CW5 DR4 DRW8	Not done
HLA Typing Husband	A3 A30 B51 CW1 CW2 DR1 DR2	Not done
Protein C	Not done	1½ times of control
MSAFP at 13 weeks (LMP & USG assisted)	**Not done**	**5.75 IU/ml (<0.15 MOM)** (Median 40 IU/ml at 13 weeks)
Fetal Autopsy	Not Applicable	Macerated still birth Firm placenta (non spongy) Wel developed sucutaneous fat layer Thymus & spleen hypoplastic
Placetal Histology	Not Applicable	Extensive fibrosis, hyalinization, infarction and narrowing as well as hypovascularity of chorionic vessel

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