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Management and outcomes of pregnancies complicated by inherited bleeding disorders

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ABSTRACT

Aim of the work was to study the obstetrical outcome and management of pregnant women with hereditary coagulation factor deficiencies. A retrospective study was carried out on 13118 pregnant women between July 2003- June 2011 at SJMCH. Women with coagulation disorders in pregnancy were identified and those with inherited coagulation factor deficiencies were selected. Their antenatal, intra and postpartum management and neonatal outcomes were analyzed. The incidence of coagulation factor deficiency in pregnant women is 0.068%. Of the 9 pregnant women with coagulation factor deficiencies, 4 had vWD, 3 had factor XIII deficiency, 1 had factor XII deficiency and 1 had factor VII deficiency. Only 1 woman was detected to have a factor deficiency at birth; 5 were detected during pregnancy; 2 at puberty and 1 in childhood. Women with factor XII and factor XIII deficiency were transfused cryoprecipitates antenatally and one prenatally. Caesarean section was performed in only 2 women. All were transfused cryoprecipitates in active phase of labor prophylactically. 2 women with vWD had primary PPH; 2 had secondary PPH, which was controlled with cryoprecipitate transfusion; one received DDAVP, progesterone and danazol. Prophylactic transfusion of factor concentrates, cryoprecipitates and adjunctive treatment can prevent pregnancy loss and PPH.

INTRODUCTION

Obstetrical hemorrhage is rarely a result of inherited coagulation defects, but they pose a great challenge in management if not diagnosed early. von Willebrand disease (vWD) is the most commonly inherited bleeding disorder with prevalence of 0.8 to 1.3 %[1].Von Willebrand factor (vWF) is essential for platelet adhesion to subendothelial collagen and formation of primary haemostatic plug at the site of blood vessel injury. It stabilizes the coagulant properties of factor VIII. Deficiency of vWF is inherited as an autosomal dominant trait. Levels of vWF raise during second and third trimester of pregnancy to 2 -3 times the baseline and fall quickly after delivery. Levels of vWF and factor VIII should be maintained at 50 IU/dl or higher during delivery and for atleast 3 days after vaginal delivery and 5 days after caesarean section [2,3].

Factor VII deficiency is a very rare autosomal recessive disorder with an incidence of 1 in 500000, in its severest form, to 1 in 350 in the heterozygous state [4, 5, 6]. It should be suspected when prothrombin time (PT) is prolonged, but APTT is normal .Bleeding diathesis does not usually clinically manifest unless level is less than 10 IU/dl [4].

Factor XII deficiency is a rare disorder whose actual prevalence is unknown, because disease is actually asymptomatic [7]. It is an autosomal recessive disorder and has been found in 4.2% women with recurrent pregnancy loss (7). It is suspected when there is an isolated prolongation of aPTT in a non bleeding child or adult. Such women usually have a trend towards thrombosis. A spontaneous increase in factor XII activity occurs in pregnancy.

Factor XIII deficiency is an autosomal recessive disorder that rarely complicates pregnancy [8]. Factor XIII is required for cross linking of fibrin molecules and stabilizing the clot as the last step in the clotting cascade. It serves as an adhesive protein during the invasion of endomentrium by cytotrophoblast and is essential just after 4-5 weeks of gestation. Its deficiency results in insufficient formation cytotrophoblastic shell ending in an abortion [9, 10]. Hence women usually presents with recurrent first trimester abortions.The level of plasma A subunit of factor XIII antigen (XIIIA ag) or Factor XIII activity (XIIIact) must be at least 2-3%, and if possible higher than 10% to prevent decidual bleeding and miscarriage [9].

Though these inherited bleeding disorders can cause obstetrical hemorrhage at any stage of pregnancy, there is scant literature regarding obstetrical management of these disorders.

We have undertaken this study to review our own management strategies and look at the pregnancy outcomes.

MATERIALS AND METHODS

A retrospective study was carried out on 13118 pregnant women between July 2003- June 2011 at SJMCH, Bangalore. Women with coagulation disorders in pregnancy such as HELLP, TTP, HUS, PHUS, ITP, liver disorders in pregnancy were identified. Only women with inherited coagulation factor deficiencies were included in this study. Antenatal and labor records were reviewed and the following aspects assessed. Age when factor deficiency was first detected, family history of factor deficiencies, occurrence of bleeding during pregnancy, mode of delivery including indication for instrumental deliveries and caesarean sections, bleeding complications in puerperium including primary and secondary postpartum hemorrhage, amount of blood and blood products transfused, neonatal outcome. The study was exempt from Institutional Review Board approval as it was a retrospective study.

RESULTS

The incidence of coagulation disorders in pregnancy was 1.29% (170 women) and that of inherited coagulation factor deficiency in pregnancy was 0.68% (9 women). Among the nine women 4 had vWD, 1 had factor VII deficiency,3 had factor XIII deficiency and 1 had factor XII deficiency. All were booked at SJMCH, Bangalore except for the woman with factor VII deficiency. Only 3 women had family history of inherited bleeding disorders. One woman with factor XIII deficiency had history of consanguineous marriage. Factor deficiency was diagnosed at birth in one women, during childhood in one women, during puberty in two women, during pregnancy in 3 women and still later in the rest of them. Antenatally two women had threatened abortion and one women presented with hematurea and gum bleeding. (Table: 1)

Only women with factor XIII deficiency received cryoprecipitates antenatally monthly or fortnightly- 1 had conceived only after 1 year of monthly cryoprecipitates. Of the 9 women 7 had vaginal deliveries and 2 underwent caesarian section for obstetric causes. One went in to spontaneous labor while six were induced with PGE2 or PGE1. Among the vaginal deliveries one was without an episiotomy and one was a pre term forceps delivery. All the women received cryoprecipitates in active stage of labor prophylactically and 2 women received it even in the immediate postpartum period. Four women received packed cells; one received whole blood as she was anemic before delivery. Of the four women with vWD, two women were given vWF during induction of labor and during delivery. In spite of this three women had primary PPH- one women had a prolonged trickle which got controlled with cryoprecipitate transfusion; two women had traumatic PPH,while the fourth woman had an uneventful delivery. Three of these women developed secondary PPH. One woman had secondary PPH 4 weeks after delivery, one on postnatal day two while the third woman developed secondary PPH on post natal day 8 and was even admitted in ICU. She was transfused 3 units packed cells and 2 units cryoprecipitates daily for 1 week. She was given DDAVP as nasal spray, Danazol, progesterones, tranexamic acid and totally 26 units cryoprecipitates for the bleeding to get controlled. None of the other women with factor deficiencies had PPH. The woman with factor VII deficiency was transfused FFP at admission, pre and post operatively. The woman with factor XII deficiency was given FFP monthly and in active phase of labor. (Table: 2) All the women were given either OCP or Mini pills or progestrones for contraception in between pregnancies.

Only 2 women were anemic at admission. All women with vWD had prolonged APTT. PT, APTT and platelet counts were normal in factor XIII deficiency. The platelet count was normal, but bleeding time was prolonged with low levels of factor VII. All the babies were healthy with good APGAR scores at delivery. (Table: 3)

DISCUSSION

This was a retrospective review of obstetric experience and outcome in women with coagulation factor deficiencies in a tertiary care hospital highlighting the need for prophylactic transfusion of blood products like Factor concentrates cryoprecipitates or FFPs and specific coagulation factors both antenatally and during labor in order to reduce ante, intra and postpartum hemorrhage. High index of suspicion to evaluate coagulation parameters in pregnancy may increase the detection rate of women with coagulation abnormalities. A complete coagulation profile consisting of venous platelet count, bleeding time PT, APTT, TT and 5 molar urea testing for clot stability is necessary.

Preconceptional counseling should be given to women with inherited bleeding disorders and the genetic implications of their disorders should be discussed. Women should be educated regarding the risk of abortions and bleeding complications and the need for monitoring of BT, APTT, PT, factor VIIIc, vWF at least in first and third trimester. It may not always be feasible to check factor levels due to paucity of diagnostic facilities and cost factor.

Early detection of factor deficiency is crucial for optimum management of pregnancy and delivery as many of these women may require prophylactic prenatal or antenatal transfusion of blood products or factor concentrates.

Emphasis must be on regular antenatal care in a tertiary care centre where blood and blood products like vWF, concentrates, DDAVP, FFP, Cryoprecipitate can be promptly given when required. Delivery must be planned in a high risk pregnancy care unit where a team of obstetrician, hematologist and neonatologist are readily available. It is important to get a preanesthetic consultation prior to the onset of labor to discuss options for regional anesthesia or analgesia.

Vaginal bleeding during first trimester has been estimated to occur in 16% of all pregnant women [1]. The next crucial period when the woman is at risk of bleeding is during labor and delivery. Since the baby is potentially at risk of bleeding, delivery should be achieved by the least traumatic method. Intramuscular analgesia should be avoided. Prolonged labor, especially prolonged II stage, should be avoided and early recourse to caesarean section should be considered [1, 2] An elective caesarian section has been recommended for type 2 and type 3 vWD to avoid bleeding complications in newborn [1] Avoid spinal and epidural anesthesia in all patients except with mild disease [1]. Plasma levels of factor XIII and vWF fall quickly after delivery and excessive bleeding may occur at this time (11).The average time of onset for PPH in women with vWD is 15.7$\pm$ 2days.(2). Desmopressin or vWF replacement therapy may be required during or shortly after delivery and first 2 to 4 weeks thereafter.

Prophylactic transfusion of cryoprecipitates in active phase of labor along with active management of III stage of labor help to

Table 1. Epidemiological features.

Case	Age	Parity	Factor Deficiency	Factor Assay	Family History	Coagulation Disorder I Detected In	Presenting complaints
Mrs.T.	27	G2P1D1	vWF	Factor 8 assay < 1 % Factor 9 assay - 88.2 % Platelet3.24lakhs/cumm BT>15' CT > 13 TT - 12.5/15 PT/INR - 20.8/1.4 APTT - 76.6/30 Urea solubility test negative	nil	I preg following IUD at 26 weeks-PPH	increased BP
Mrs. P.	26	Primi	vWF	Factor 8 assay - 5.5%	nil	15 years of age- puberty, menorrhagia and bleeding gums	labor pain
Mrs. Y	21	Primi	vWD	Factor 8 assay-5%	NIL	13 years of age ; puberty menorrhagia	safe confinement
Mrs H	25	Primi	vWD	Factor 8 assay – 2.7%,vWF-1.8% BT-12', PT/INR-12/1.2 APT T-70.7/30	Father has vWD	10 weeks of gestation	safe confinement
Mrs. S	27	G3P1L1A1	factor VII	BT-3'30CT-9'30 PT/INR 104/8.2 APTT-32/31 Mixing study PT-15.4	nil	present admission	hematuria, gum bleeding
Mrs S	24	G2P1D1	Factor XII	PT/INR-10/0.9 APTT-52.9/30 APLA- Negative	Nil	24 weeks gestation	Increased BP
Mrs. SK	35	G9P1L1A7	Factor XIII	Urea Solubility test for Factor 13 positive.	nil	6th pregnancy during work up for reccurent abortion	spotting PV
Mrs. B	29	G7A6	Factor XIII	Urea Solubility test for Factor 13 positive.	sister has F XIII def	child hood at 7 years of age; extradural hemorrhage following trivial trauma to head	leak PV
Mrs. TS	29	G2P1D1	Factor XIII	Urea Solubility test for Factor 13 positive.	father brother have F XIII def	from birth, excess bleeding from umbilical cord	increased BP

limit PPH. The aim of prophylactic transfusion is to raise factor levels to cover labor, delivery and post natal period. In women with vWD risk of primary PPH has been found to be 16 to 29 % (2) while that of secondary PPH is 20-29 % [2, 12, 13] We have effectively managed moderate to severe vWD with intrapartum use of 3 to 4% trough levels of Anti Haemophilic factor. While the general recommendation to maintain 30- 40% trough levels of Anti Hemophilic Factor intrapartum and for 5-7 days postpartum. DDAVP has been reported to be safe and effective in preventing significant bleeding at delivery [14)]

FFPs are the mainstay of management in women with factor VII deficiency due to easy availability and less thrombogenic potential over prothrombin complexes and other concentrates. However, it carries with it the risk of transmission of blood borne viruses. Frequent transfusions are necessary and potentially large volumes of frozen plasma may be required to maintain haemostasis, as the half life of factor VII is relatively short (4-5 hours). Despite this short half life FFP is efficient in preserving

Table 2. Complications, treatment and pregnancy outcome

Case	GA at termination of pregnancy (weeks)	Antenatal Complications	Antenatal Treatment for factor deficiency	Mode of delivery	Blood Products Transfused Intrapartum	Post Partum Complications-Primary PPH	Secondary PPH	Neonatal Out Come
Mrs.T.	36+6	Mild Pre eclampsia	nil	FTND with out episiotomy	6 units cryoprecipitate 900U vWF	prolonged trickle blood loss 300 ml	Nil	healthy 1.81 kg girl AP1'-8/10 5'9/10
Mrs. P.	39	nil	nil	FTND with RMLE	15 units cryoprecipitate 2 units Packed Cell	Traumatic PPH,EUA cervical laceration sutured under GA	4 Weeks After Delivery Treated with 44 units Cryoprecipitates	Healthy 2.7kg, girl 1'-8/10, 5'-9/10
Mrs. Y	38+2	Nil	nil	FTND with RMLE	8 units cryoprecipitate inj vWF 1 at induction, 1 at delivery	nil	Sec PPH on PND8 3 units Packed Cell, 2 units cryoprecipitates daily for 1 wk, total 26 units cryo precipitate given DDAVP 2 puffs nasal spray Danazol, Progesterones, Tranexamic acid given	healthy 2.75 kg boy 1'-8/10, 5'-9/10
Mrs H	40+1	Nil	Nil	FTMD with RMLE	21units cryoprecitates	Prolonged trickle,para urethral tear	Sec PPH on PND2- total 34 units of cryoprecipitates given	Healthy 3.39kg girl 1'-8 /10,5- 9/10
Mrs. S	37+2	hematuria, gum bleeding, hypothyroidism	vit K and cryoprecipitate during this hematuria	elective FTCS-indn prev CS+ fac VII def	12units cryoprecipitate 1 unit Packed Cell	nil	nil	healthy 2.8kg girl 1'-8/10 5'-9/10
Mrs.S	37+1	Intrahepatic Cholestasis,CMV IgM+, preeclampsia	1unit FFP/ Month	FTND with RMLE	5 units FFP	nil	nil	Healthy,2.95 Kg boy, 1'-8/10, 5'10/10
Mrs. SK	35+6	DADC twins,Pre eclampsia, bronchial asthma admit at 5 th month with fever and bronchial asthma	2 units cryoprecipitate fortnightly since 7 weeks of gestation	emergency LSCS ind- breech,twins, Pre eclampsia, NRNST,reduced FM,BOH	16units cryoprecipitate 1 unit Packed Cell	nil	Nil	I- Boy 2.05kg II- boy 2.42kg both healthy 1'-8/10, 5'-10/10
Mrs. B	35+5	threatened abortion and anemia at 19+5 weeks,Rh -ve preg, ICT -ve	2 units of cryoprecipitate fortnightly Antenatally &prenatally	preterm forceps delivery with RMLE	6 units cryoprecipitate 1 unit Packed Cell 1 unit Whole Blood	nil	nil	5'10/10 Healthy 2.39kg girl 1'-8/10, 5'-9/10
Mrs. TS	38	Pre eclampsia	2 units cryoprecipitate monthly	FTND wtih RMLE	4 units cryoprecipitate	nil	nil	Healthy 1.79kg girl 1'-8/10, 5'-9/10

Table 3. Comparison of blood parameters

Sl. number	Lab values							
	At admission				At discharge			
	Hb (gm/dl)	Platelet (lakhs/cumm)	PT/INR	APTT	Hb (gm/dl)	Platelet (10^5/cumm)	PT/INR	APTT
Mrs.T.	10.3	2.7	10.2/0.8	57.3/30	9.2	1.5	10.5/1	50.3
Mrs. P.	11	2.2	10.4/0.8	51/30	10.1	1.8	11/1.1	45.1
Mrs. Y	12.9	2.2	12.6/1	52.3/30	11.8	2.5	12/0.9	44.5
Mrs H	10.5	1.49	12.6/1	36/30	10	1.4	12/1	36.2
Mrs. S	11.3	1.9	104/82	32/31	9.4	2.2	18.8/1.5	30.1
Mrs S	11.9	2.2	10/0.9	52/30	11.3	2.1	9/.7	29.2/30
Mrs. SK	12.3	1.6	15/1.5	26/34	8.6	1.5	15/0.9	28
Mrs. B	8.8	2.59	11.5/0.9	22.2/30	9.6	1.3	11/0.09	26
Mrs. TS	9.3	2.2	10.2/0.8	27.1/28.5	8.6	1.8	11.1/0.9	29

the coaguability of blood or reversing the hemorrhagic diasthesis because levels as low as 10% of normal can bring about haemostasis [4].

Factor VII concentrates are more thrombogenic and carry greater risk of viral transmission as they are pooled aggregates. Recombinant factor VIIa is produced by recombinant DNA technology is less thrombogenic and does not carry the risk of viral transmission [4]. It has been successfully used to tackle bleeding diasthesis but availability and high cost are major hurdles in using it.Inherited factor XII deficiency is a very rare disorder that usually requires no treatment as most of these women can withstand severe challenges to the hemostatic system(6). Anti thrombotic precautions need to be taken as it can cause a hypercoaguable state.

Clotting inhibitors and antibodies to factor XII have been implicated to cause recurrent pregnancy loss in woman with antiphospholipids syndrome. Hence they should be considered second step of thrombophilia screening in recurrent pregnancy loss especially if a persistant prolonged aPTT is present without an apparent cause (6). Antenatal and intrapartum transfusion of FFP can prevent pregnancy losses due to factor XII deficiency and ensure a good neonatal outcome Factor XIII deficiency should be considered in women with recurrent pregnancy loss even if they do not present with coagulation pathologies. Substitution therapy with either factor XIII concentrate or FFP results in successful pregnancy outcome [15]. Prophylactic cryoprecipitate transfusions antenatally can prevent such miscarriages [14]. Factor XIII A concentrates is better than FFP or cryoprecipitate but are expensive and hence impractical in our setting. No replacement therapy is necessary in puerperium because it is usually uneventful without it [9].Cryoprecipitate transfusion is recommended during post operative period and at the time of suture removal to enhance wound healing. All the babies were healthy at delivery and discharged between postnatal days 5 to day 10.

CONCLUSION

In developing countries where factor concentrates, though preferred, but out of reach due to high cost and limited availability, coagulation defects can be successfully managed with prophylactic transfusion of FFPs and cryoprecipitates.

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