HYPOFIBRINOGENEMIA*

CASE REPORT OF A SEVERE CASE

by

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Fibrinogen deficiency is a rare condition in obstetrics. De Lee recognised it in 1901 but called it a haemophilia-like disease. Dieckmann first drew attention to this condition from the point of view of etiology in 1936, and Moloney et. al. subsequently, in 1949, treated a case with intravenous fibrinogen. Reid aand Weiner published an interesting case report in 1953.

The pathogenesis of this syndrome is still an unsolved riddle and several theories have been advanced, but none is proved. Consequently management of such cases still is a problem. The rarity of the condition makes individual experience very limited. Hence we present this case. This is the third case in this hospital during the last ten years, but the first one which carried through the crisis successfully.

CASE REPORT

Mrs. F. P., Muslim, aged 30 years, was brought to this hospital on 8-5-62 at 1 P.M. for

1. Frank painless haematuria of 7 days' duration and
2. with H/O 9 months' amenorrhoea. On further questioning it was found that
3. There was no increase in girth of abdomen and
4. No foetal movements were felt for the previous two months.

The patient was treated elsewhere for haematuria with coagulen Ciba, vitamins C and K and calcium gluconate for 8 days. There was no history of any drugs taken recently which could account for the haematuria. The medical history was not relevant.

Inquiry about the present pregnancy did not suggest any pathology perior to the previous two months. She was a 5th para, and had 4 full-term normal deliveries with normal ante-natal and post-natal periods. The last delivery was 5 years ago. There was no history of ante-partum or post-partum haemorrhage during past pregnancies.

On Examination: The patient was well built and well nourished, with a mild degree of anaemia. She had patches of ecchymosis over the right upper arm and lateral aspects of both thighs. There was no oedema of the feet. Blood pressure was 112/80 mm. Hg.

Abdominal examination revealed 24 weeks' size of uterus. Foetal parts were not palpable and foetal heart sounds were not heard.

Per vaginal examination, cervix admitted the tip of the finger. The presenting part was high up and not within reach of the finger.

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RELEVENT EVENTS

TABLE No. 1

KEY: *BT*: *Blood Transfusion* 350 *cc.*
HF: *Human Fibrinogen*

Date	Time	WEINER'S TEST	Haema-turia	Other Features	Plasma F mgm./	Treatment
8-5-62	8.00 p.m.	No clot formation	Frank	Hb 64%	—	Coagulen Ciba; vitamin C & K; Calcium B.T. (1).
9-5-62	2.00 p.m.	No clot formation initially; formed in 15 minutes which dissolved afterwards	Frank	Hb 60%	—	As above plus B.T. (2).
	6.00 p.m.	-do- -do-	-do-	—	—	H.F. intravenous (3.0) Gms.
	8.00 p.m.	Clot appeared in 5 minutes 30 secs. but fragmentation and dissolution afterwards	-do-	T 103°F & rash after H.F.	—	Antiallegrgic; Diaphoretic line of treatment—Injection Penicillin and Strepto BD.
10-5-62	1.00 a.m.	Clot appeared in 6 minutes but no retraction	Blood stained sediment	Hb 54%	9	B.T. (3).
11-5-62	1.30 p.m.	-do- -do-	-do-	According to antibiotic sensitivity reports—Ter-	—	Inj. Terramycin 100 mg. im. 6 hourly 250 c.c. double strength plasma (2).
	4.00 p.m.	-do- -do-	-do-	ramycin	—	250 c.c. double strength plasma (4).
12-5-62	8.30 a.m.	Clot formation in 4 minutes 30 secs. and retraction observed	-do-	Hb 56%	—	B.T. (4).
	4.30 p.m.	-do- -do-	-do-	—	—	250 c.c. double strength plasma (6).
	7.30 p.m.	Clot formation in 5 minutes and retraction present	-do-	Two drips started	—	i. Pitocin 10 i.u. in Oi (total 20 i.u. before evacuation). ii. 250 c.c. double strength plasma (8).

Date	Time	WEINER'S TEST		Haema-turia	Other Features	Plasma F mgm./	Treatment
13-5-62	3.05 a.m.	Clot formation in 4 minutes and clot retraction present		Pink	Patient delivered a female still-born; placenta and membranes intact; showing sclerosis—uterus atonic-blood trickle plus pulse 90/m. B.P. 86/60 mm. Hg.	—	Pitocin 10 i.u. in O1 plus Injection methargin one amp. i.v.
	8.00 a.m.	-do-	-do-	-do-	Blood trickle present Ut: contracted	—	Quadruple strength 250 c.c. plasma (12).
	4.00 p.m.	-do-	-do-	-do-	—	—	B.T. (5).
	6.00 p.m.	-do-	-do-	-do-	—	—	B.T. (6).
14-5-62	8.00 a.m.	-do-	-do-	Clear	Blood trickle present	20	Observation.
15-5-62						62	
16-5-62						70	
17-5-62						140	
19-5-62						160	
21-5-62						230	
23-5-62						350	
24-5-62						390	
25-5-62						370	

Investigations

1. Urine showed frank haematuria.
2. Blood picture, Hb 64%, W.B.C. 9,600/cmm., P. 88%, L. 11%, E. 1%.
3. Blood group A Rh positive. The puncture site bled for about 4 minutes and a small haematoma formed around it.
4. Bleeding time, 3 min. 30 secs. Clotting time 7 minutes.
5. Hey's test was done and was negative.
6. Platelet count 1,50,000/cmm.

The patient was put on routine conservative treatment for a bleeding disorder viz. Coagulen Ciba, vitamins C and K, pot. citrate mixture, slow blood transfusion, intravenous calcium; temperature, pulse and respiration and amount of haematuria were observed. A plain x-ray of abdomen was taken and demonstrated a foetus showing Spalding's sign. Clot observation test was done. Blood failed to clot even after 2 hours.

Diagnosis of hypofibrinogenemia of severe degree was arrived at 10 P.M. on 8-5-62 and blood bank was requested to keep at least 4 pints of blood ready. On 9-5-62, we could start our treatment with one bottle of human fibrinogen which contains 3 grams of fibrinogen approximately. The patient was observed round the clock day and night; follow up in Table No. 1 mentions the critical events only. Our follow up and line of treatment mainly depended upon "Weiner's Test" although repeated Serum-Fibrinogen estimations were done.

Other Investigations done were:

1. Serum proteins — total 7.6., grams-alb. 3.2 G., glob. 4.4 A/G: 1/1.3.
2. Serum calcium 9.5 mgm%.
3. Blood urea nitrogen 12 mgm%.
4. Van Den Berg was negative. Icteric Index 2. Serum bilirubin within normal limits.
5. Prothrombin time 26 sec., (control 18 sec). Prothrombin index 69%.

It is clear fom Table 1 that when the labour was induced by pitocin drip blood fibrinogen level was only 20 mgm% but our management was guided by Weiner's test.

Fibrinogen variations in health and disease

Amount of fibrinogen present in blood of an adult female varies from 220-400 mgm%. During pregnancy it may vary from 300-600 mgm%. Plasma fibrinogen concentration rises during first trimester of pregnancy, remains at this elevated level during the second trimester and reaches a peak in the third trimester. It falls to control levels by 6th post-partum week, which coincides with duration of puerperal period. The critical level varies from 100 to 150 mgm% while haemostasis is secured at a level of 200 mgm%.

Table No. II

Summary of the present Case

Plasma Fibrinogen before therapy	Total Fibrinogen in G			Foetus	Mode of delivery	Comments
	H.F.	Blood Fib.	Pl. Fib.			
9 mgm%	One Bottle	Six Bottles	Twelve Bottles	Female still-born	Induction with i.v. pitocin total of 30 i.u.	Management guided by Weiner's Test
	3 G	5.2 G	6.6 G			
		14. 8 G				

Discussion

Hypofibrinogenemia has been associated with the following conditions.

1. *Intrauterine Death*

It has been reported that hypofibrinogenemia occurs when a dead foetus of more than 12 weeks' gestation is retained in utero for over 4 weeks, usually, but not always, by Rh -ve sensitized mother. (Barnes).

Such cases have been observed in occasional cases of Rh-ve patients when the foetus died of Rh incompatibilities and was retained in utero for several weeks. In this instance hypo-fibrinogenemia was not interpreted as being related to the Rh factor but rather as a consequence of retention of the autolized products of conception with release of thromboplastic substance from decidua and placenta. (Reid and Weiner).

2. *Amniotic Embolism*

Uncontaminated amniotic fluid collected during labour contains a coagulant that behaves like thromboplastin and has ability to reduce the clotting time of haemophilic from 54 to 4 minutes. Amniotic fluid however does not contain fibrinogen, thrombin or fibrinolysins. (Reid and Weiner).

On the basis of these observations it was suggested that thromboplastic material in amniotic fluid, as it gained entrance into systemic circulation, would defibrinate the blood and cause uterine haemorrhage; the auto-infusion of this amniotic fluid into the blood stream effecting defibrination, similar to that seen when thromboplastin is infused into an experimental animal.

3. *Couvelaire Uterus*

Severe cases of accidental haemorrhage are associated with this condition. Fibrinogenemia invariably follows separation and never precedes it; (Larkin). Findings like free blood in the peritoneal cavity, broad ligament haematomas, retroperitoneal clots may be due to hypofibrinogenemia.

4. Hypofibrinogenemia does occur in about 5-10% cases of *placental separation;* but it is sufficient to cause deficient coagulation in only 2-4% of cases. (Weiner Reid and Roby).

5. *Cl. Welchii Infections*

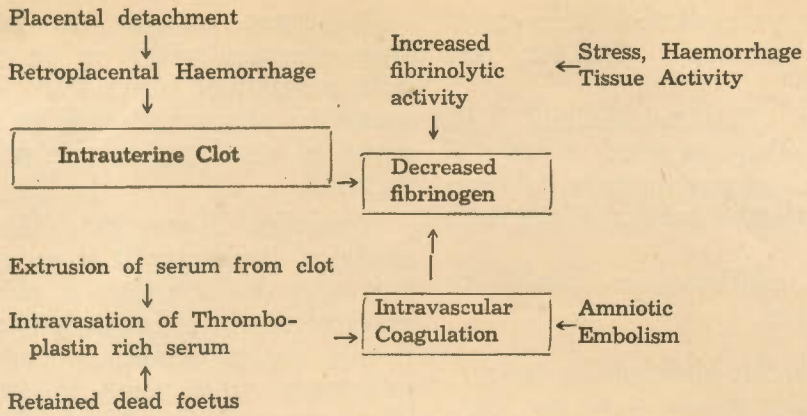
Especially in post-abortal sepsis. Pritchard believed that hypofibrinogenemia was due to liver damage from haemolysis.

6. Hypofibrinogenemia is sometimes associated with *mis-matched blood transfusion.* (Madry).

7. Cases of *secondary post-partum haemorrhage* are the cases which deserve attention. Whether the bleeding is due to infection of the retained material or due to hypofibrinogenemia should be found out.

8. Role of *various hormones* on regulation of fibrinolytic activity of blood during pregnancy is really uncertain. (Madry).

Composite scheme depicting the multiple mechanisms invloved in etiology of hypofibrinogenemia. (Reproduced from "Madry's").



Aetiopathology

1. *The theory of causation put forwards by Schneider's* (1951). This postulates that intravascular deposition of fibrinogen as fibrin occurs on liberation of thromboplastin from the uterus — is generally accepted as workable hypothesis.

The liver has no role to play in this hypothesis.

Thromboplastins liberated from damaged decidua and chorion + Prothrombin → Thrombin

Thrombin + Fibrinogen → Fibrin forms the clot

in general arteriolar bed causing fibrinogen deficiency in circulating blood.

2. *Possibility of fibrinolysis by fibrinolysins has been suggested.* It has a definite role to play but there are several factors affecting that. (Reid & Weiner).

3. *Sometimes there are multiple coagulation defects* viz. thrombocytopenia, hypoprothrombinemia, fibrinolysin factors etc. (Madry).

4. *Fibrinogen deposition in placenta* has been reported but there is no significant co-relation between plasma fibrinogen determination and placental fibrin formation. (Norboum).

Clinical features

1. The patient might be brought to the hospital for antepartum haemorrhage or post-partum haemorrhage (either primary or secondary), bleeding from puncture sites, ecchymosis, or haematemesis or epistaxis. Our case presented as haematuria.

2. There may be an associated history of either
   1. Accidental haemorrhage
   2. Intrauterine death or

3. Amniotic embolism; like respiratory difficulty, shock, convulsions, coma. In such a case the patient may die of embolism or may survive to die of ante-partum or post-partum haemorrhage if fibrinogenopenia is not recognised and treated. The patient is usually a multipara; over the age of 30 years and usually there is premature rupture of membranes and vigorous labour either

natural like precipitate labour or induced by pitocin. (Steiner and Lushbaugh).

Diagnosis: It is not difficult if its possibility is kept in mind in cases of antepartum and post-partum haemorhage, intrauterine death and amniotic embolism.

Positive confirmation could be obtained from

A. *Weiner's clot observation test:*

When blood drawn from the antecubital veins fails to clot then plasma fibrinogen level is below critical. When clot appears but is followed by fragmentation it is suggestive of marginal levels.

B. *One minute test:*

Here 0.2 c.c. each of citrated blood and freshly prepared thrombin solution are mixed together.

a. when clotting occurs in 5-10 secs., clot is firm in 60 secs. and later when the clot contracts — findings are perfectly normal.

b. when there is delay in clotting beyond 15-20 secs., liquifaction or dissolution of clot by 60 secs., this is evidence of hypofibrinogenemia.

c. when there is total absence of clot formation in 60 secs., this is definite evidence of afibrinogenemia.

C. *Plasma fibrinogen estimations:*

The exclusion of other dyscrasias is also an important part of the investigations.

Hey's test and platelet count should be done to diagnose associated thrombocytopenia or to exclude it.

2. Prothrombin time and Index from point of view of hypoprothrombinemia.

3. Serum calcium to rule out hypocalcemia which is so common with pregnancy. Lees from Sheffield mentions about one case he lost because of not keeping this possibility in mind.

Remedial Measures: From the study of literature it is an accepted fact that defibrination is often progressive until patient is delivered and it may be impossible to correct the deficiency, until then a circulating fibrinogen is being taken away from blood very quickly.

The aim of treatment should be to correct fibrinogen deficiency before delivery and certainly a main reserve must be held for use at the time of delivery, though only correction of plasma fibrinogen has sometimes been sufficient and normal spontaneous evacuation occurred afterwards.

There are two important factors in the treatment viz. cost and availability. As soon as a case is diagnosed plenty of fresh blood and plasma should be made available.

1. Usually about 2 to 10 grams of fibrinogen is sufficient. Reid in his first published case used 24 grams of fibrinogen. It is convenient to remember the fibrinogen contents of different products — one pint of fresh blood contains 1.4 grams of fibrinogen approximately. Quadruple strength plasma, pint one, contains about 4.4 grams of fibrinogen. One bottle of human fibrinogen contains approximately 3 g. fibrinogen.

2. Artificial rupture of membranes reduces intrauterine tension, prevents further placental separation, reduces thromboplastin absorption, and there is less likelihood of anuric renal

failure. (Weiner, Reid and Roby and David Lees).

Artificial rupture of membranes should be followed by pitocin drip in high concentration; anywhere from 40-200 I.U. may be required. For the present case 30 i.u. were sufficient to induce labour and cause evacuation.

3. Prophylactic ergometrine should be given at the end of 2nd stage of labour.

Hot intrauterine douche has its advocates as they claim that heat improves the clotting process locally.

4. Fibrinogen has an important role to play in the *body defence mechanism* hence all precautions should be taken to avoid sepsis and suitable antibiotic should be started from the beginning as a routine.

5. There is known antagonism between heparin and thromboplastin and one would suggest controlled administration of heparin for prevention of intravascular clotting.

6. Role of hysterectomy: Hysterectomy should rarely be necessary but it has its own place in management, especially when

(i) defibrination process is severe, progressive with no prospects of early delivery.

(ii) likelihood of further antepartum and severe post-partum haemorrhage occurring.

Advantage in these circumstances is that the main source of bleeding and main source of thromboplastins has been removed.

As 'David Lees' puts it 'Hysterectomy is a calculated therapeutic risk to replace uncertain risks and it allows accurate timing in administration of fibrinogen so that danger period can exactly be covered.'

Larkin and Philipp have reviewed a case in 1957 where the condition was treated with lower segment caesarean section and the usual measures for correcting hypofibrinogenemia.

Selection of line of treatment for present case

In the case detailed above there was no foetal interest for consideration as foetal death was confirmed clinically and by X-rays. On admission blood failed to clot and derangement of clotting mechanism to this extent guided us to improve the clotting mechanism to some extent before attempting the evacuation and thus to avoid the likely fatal haemorrhage.

Although the role of artificial rupture of membranes has been stressed enough, similar procedure was not followed in this case as it was likely that, with two months' foetal death, membranes would have been autolized. Introduction of sepsis and its spread was also another point in consideration.

It was thought suitable to effect evacuation per vaginam only, as oozing from the abdominal wound also could have become uncontrollable. However, uterine bleeding could be controlled with oxytocics e.g. ergometrine, and thrombin pack, or a rapid hysterectomy, if found necessary.

Summary

1. A case of severe hypofibrinogenemia has been reported.

2. Present knowledge of etiology, pathology, clinical features and reme-

dial measures has been discussed.

3. Close co-operation between pathologist and obstetrician has been stressed.

4. Place of hysterectomy as life-saving measure has been stressed.

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