Haematological problems

Coagulation disorders

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The risk of severe haemorrhage in pregnancy is well recognized, and uncontrolled bleeding remains a major cause of maternal death throughout the world, including the British Isles. The haemochorial system of human placentation carries with it an inherent risk of haemorrhage and this probably explains why the serious congenital disorders of haemostasis are predominantly found in the male. In pregnancy, complex physiological changes occur in the systems responsible for the control of blood loss from the vascular tree.

Coagulation and Fibrinolysis during Normal Pregnancy

COAGULATION SYSTEM

The effect of pregnancy on the clotting factors can be detected from as early as the first trimester. Plasma fibrinogen gradually increases and levels ranging between 400 mg and 600 mg per cent are usually present in late pregnancy and labour. This elevation of fibrinogen is much greater than occurs in women taking high doses of oestrogen and progestational steroids, and is thus not explained by the effect of these hormones. Factors VII and X likewise show a definite increase and in the third trimester are usually in the range 120-180 per cent. Cold-promoted activation of factor VII when the plasma is exposed to low temperatures for almost 20 hours is a phenomenon which can readily be shown in the plasma of pregnant women and in women using oestrogen/progestogen contraception; factor VII activity is enhanced as much as ten-fold and activation may be mediated through the kallikrein system (Gjønnaess, 1973).

Factor VIII, as measured by two-stage techniques, has an average value of around 200 per cent in late pregnancy, with a range from 80 to 450 per cent. During pregnancy, Bennett and Ratnoff (1972) found that factor VIII-related antigen (factor VIII-RA) increased in proportion to factor VIII activity, but our own investigation and that of Bouma *et al* (1973) showed that the ratio of factor VIII-RA to factor VIII activity, as measured by a clotting assay,

slightly increased during pregnancy and the ratio was considerably higher in patients with severe pre-eclampsia. An increase of factor VIII activity during pregnancy has also been noted in women with congenital deficiency of factor VIII, as found in some carriers of classical haemophilia and in Von Willebrand's disease. Postpartum haemorrhage is a common complication in women severely affected by these congenital deficiencies, particularly where the factor VIII level is seriously depressed and does not increase during pregnancy. In such patients, the administration of factor VIII concentrates or fresh plasma before delivery and during the first three or four days of the puerperium will obviate the risk of uterine haemorrhage.

Several authors have reported slight elevations of factor IX during pregnancy. Studies on factor XI reported a decrease during pregnancy, with average levels between 60 and 70 per cent (Nossel *et al*, 1966). The level of fibrin-stabilizing factor (factor XIII) was investigated by Coopland *et al* (1969) and a gradual decrease was found during pregnancy with the levels falling to about 50 per cent at term. An increase in the level of factor XII and a decrease in antithrombin III was reported by Biland and Duckert (1973); in the author's laboratory a small decrease in the levels of coagulation inhibitors, antithrombin III and anti-factor Xa were found during normal pregnancy.

FIBRINOLYTIC ENZYME SYSTEM

Profound changes occur in the components of the fibrinolytic enzyme system during pregnancy. The level of plasminogen substantially increases and the rise appears to parallel that of fibrinogen (Bonnar *et al*, 1969b). Fibrinolytic activity in plasma also decreases markedly during pregnancy, and Åstedt (1972) found that the high fibrinolytic activity which normally occurs in blood in response to venous occlusion diminished progressively during pregnancy. In vein biopsies during pregnancy Åstedt (1972) found that the fibrinolytic activity in the vessel walls decreased significantly. The placenta has been shown to contain inhibitors which block urokinase-induced

fibrinolysis (Kawano *et al*, 1968; Uszynski and Abildgaard, 1971).

FIBRIN/FIBRINOGEN DEGRADATION PRODUCTS (FDP) AND SOLUBLE COMPLEXES

An increase of FDP in parallel with gestation was reported by Woodfield and colleagues (1968), but in other studies no consistent increase was found in healthy pregnancy or was shown to occur in only a proportion of pregnant women (Bonnar *et al*, 1969a; van Royen, 1974). Hedner and Åstedt (1970) investigated FDP levels in serum and urine of 1000 women in the third trimester. None of the women had FDP in the urine and of 99 who had increased FDP levels in the serum 85 per cent had conditions such as preeclampsia, hepatitis and Rh-immunization.

In a recent study, McKillop *et al* (1976) reported significantly increased concentrations of soluble fibrin/fibrinogen complexes during normal pregnancy when compared with age-matched non-pregnant controls. In our studies of heparin tolerance during pregnancy we also found that when heparin was

Fig 1 Plasma heparin levels in a patient during pregnancy given subcutaneous heparin; 10 000 units of subcutaneous heparin were required in late pregnancy to produce similar plasma levels to that achieved by 5000 units of subcutaneous heparin in early pregnancy.

given by subcutaneous injection a higher dosage was required in the third trimester, compared with the first trimester, to achieve similar blood levels (figure 1). This would suggest that an increased ability to neutralize heparin is a feature of the latter half of normal pregnancy.

Intravascular Coagulation and Normal Pregnancy

The above evidence strongly suggests that intravascular coagulation is a physiological phenomenon of a normal pregnancy. Using electron microscopy, fibrin deposition can be clearly demonstrated in the maternal vascular channels supplying the placenta

(Sheppard and Bonnar, 1974). This local process of intravascular coagulation will result in a low-grade continuous consumption of clotting factors which will stimulate a compensatory increase in synthesis. The resulting increased levels of fibrinogen and coagulation factors in the circulating blood will be advantageous to meet the sudden demand for haemostatic components which arises during placental separation when a blood flow of 500 to 800 ml per minute to the placental site has to be staunching by the combined effects of myometrial extravascular compression and explosive fibrin deposition.

Preeclampsia

In women who develop severe preeclampsia a common finding has been a reduced number of circulating platelets and an increase in the levels of serum FDP. The FDP levels are also substantially elevated in the puerperium in patients who have had preeclampsia. In a study of primigravid women who developed preeclampsia, Condie (1975) showed that urinary FDP was substantially higher during the first 24 hours after delivery than in normal pregnancy and a significantly increased urinary output of FDP was still present six days after delivery. In a serial study of over 200 pregnant women, of whom 10 developed clinical and biochemical evidence of severe preeclampsia, we found that the deviation from the levels of normal pregnancy for both the platelet count and serum FDP occurred around 24 weeks' gestation (figure 2). As shown in figure 3, the ratio of factor VIII RA to factor VIII activity was markedly increased in women with preeclampsia. The levels of soluble fibrin/fibrinogen complexes were also shown to be higher in patients with preeclampsia than in normal pregnancy (McKillop *et al*, 1976). These findings indicate that thrombin activity is considerably greater in pregnancies complicated by preeclampsia.

We have investigated the use of heparin in patients with preeclampsia and evidence of diffuse intravascular coagulation, as shown by high levels of serum FDP and thrombocytopenia. The administration of heparin (10 000 units 12-hourly) and dipyridamole (200 mg 6-hourly) was followed by a lowering of the FDP levels and a return of the platelet count to normal, but despite this no change was evident in the clinical course of the preeclampsia (figure 4). Whatever the trigger, the evidence indicates that in preeclampsia an increased generation of thrombin and intravascular coagulation occurs as compared with normal pregnancy, and this phenomenon occurs *pari passu* with the disease process.

The two organs intimately concerned with the syndrome of preeclampsia are the uterus and the

Fig 2 Comparison of the levels of serum fibrin/fibrinogen degradation products (FDP) and the platelet count in 10 pregnant women who developed severe preeclampsia, compared with 20 women who had a normal pregnancy (mean + standard error).

Fig 3 Ratio of factor VIII-related antigen to factor VIII activity during normal pregnancy and in 10 patients who had severe preeclampsia.

kidney. Of these, the uterus and its contents are primarily involved, as evidenced by the dramatic effect of delivery or fetal death. The original concept of diffuse intravascular coagulation was derived from studies in experimental animals where disseminated fibrin deposition was readily shown. In preeclampsia it is much more likely that the changes detected in

Fig 4 Intravascular coagulation associated with severe preeclampsia treated with subcutaneous heparin and dipyridamole. Despite correction of intravascular coagulation, as shown by the falling levels of FDP and rising platelet count, no change was evident in the clinical course of the preeclampsia.

the peripheral blood are a reflection of localized fibrin deposition, particularly in the uteroplacental circulation and in the kidney. The fact that heparin therapy will not reverse established preeclampsia does not exclude intravascular coagulation as having an important role in the pathogenesis of the disease. A controlled study of low-dose heparin and an anti-platelet agent throughout the second half of pregnancy in a high-risk group would be of considerable interest. On available evidence, abnormal fibrinogen metabolism could still be the major pathway through which the syndrome of preeclampsia is mediated.

Acute Coagulation Defects in Obstetrics

The obstetric complications in which diffuse intravascular coagulation and defective haemostasis may arise are shown in the table. A large number of tests are available for diagnosing coagulation failure in the obstetric patient, but given the emergency nature of the clinical situation time-consuming assays are of little value in clinical management. The most useful screening tests are those concerned with the level and ability to clot of the plasma fibrinogen and with the platelet count. As bedside procedures, the whole blood clotting time and the thrombin clotting time are recommended. The fibrinogen 'titre', which can be performed in citrated blood, is of value for providing a rapid estimate of the level of plasma fibrinogen.

Complication
Abruptio placentae
Amniotic fluid embolism
Eclampsia and preeclampsia
Induced (saline) abortion
Retained dead fetus or missed abortion
Intrauterine infection:
Septic abortion
Ante- and postpartum infection
Hydatidiform mole
Placenta accreta
Rupture of the uterus
Prolonged shock of any aetiology
Transfusion of incompatible blood
Severe fetomaternal bleeding

Table Complications associated with diffuse intravascular coagulation and defective haemostasis

The platelet count will reflect, not only the degree of intravascular coagulation, but also the effect of the transfusion of a large quantity of banked blood. Where delivery of the patient is not imminent, low levels of circulating platelets, eg, less than 30 000 per cmm, emphasize the need for obtaining supplies of platelet-rich fresh blood or platelet concentrates.

ABRUPTIO PLACENTAE

This is by far the commonest cause of serious coagulation failure and, in general, the greater the degree of placental separation the more likely defective haemostasis. The severe concealed or mixed variety of abruptio placentae is practically always accompanied by diffuse intravascular coagulation with reduced levels of coagulation factors and increased levels of FDP. The depletion of fibrinogen in abruptio placentae is well recognized, but is often overemphasized to the neglect of the other essential haemostatic components. In patients with severe abruptio placentae we have found factor VIII activity as low as 10 per cent with the factor VIII RA at 300 per cent. In a series of 15 patients with severe abruptio placentae and coagulation failure no evidence of pathological fibrinolytic activity was detected. The high levels of FDP which are present are most likely due to breakdown of intravascular fibrin by local release of activator. High levels of FDP, as well as being a major factor in defective haemostasis, will also have a beneficial role in inhibiting the process of fibrin deposition within the vascular tree.

Placental separation at normal delivery is usually rapid and the associated activation of the clotting system is largely confined to the uterine circulation. In abruptio placentae, partial or complete separation of the placenta occurs, usually before the patient is in labour, and this situation is maintained until the process of labour and delivery is complete. During this time, a substantial blood flow continues to the

uterus and the placental site, allowing the entry of procoagulant substances into the systemic circulation from the damaged placenta and decidua. The process of intravascular coagulation is therefore likely to continue until the placenta is delivered and the uterus empty and retracted.

Shock will also promote intravascular coagulation and the rapid and adequate correction of the depleted blood volume by monitoring of the central venous pressure and the urinary output will therefore be a major factor influencing the process of intravascular fibrin formation. Where serious haemorrhage and defective coagulation are present, the transfusion of fresh blood to maintain the circulating blood volume will be the best management. If fresh blood cannot be obtained, then fresh frozen plasma rather than concentrated fibrinogen should be given; this will provide a supply of factors V and VIII as well as fibrinogen and the coagulation inhibitor

Fig 5 Abruptio placentae with defective blood coagulation. Antithrombin III showed a marked decrease during infusion of concentrated fibrinogen.

antithrombin III. When the concentrated fibrinogen is given alone, we have found a sharp decrease of antithrombin III which suggests that the fibrinogen concentrates may aggravate the intravascular coagulation (fig 5).

In the presence of a severe abruptio placentae with a dead fetus, the aim should be to expedite vaginal delivery, avoiding any soft tissue damage to the genital tract. The delivery of the fetus and placenta is usually followed by spontaneous correction of the

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coagulation defect and until such time as this occurs myometrial retraction will greatly reduce bleeding from the placental site. In severe abruptio placentae with a dead fetus, delivery by caesarean section is rarely indicated, and in the presence of a coagulation defect the danger of bleeding from surgical incisions, especially following operation, must be appreciated. In the vast majority of cases, conservative management with maintenance of the blood volume will be followed by spontaneous delivery. In the exceptional case where this does not occur and defective clotting is present, any operative interference should be delayed until normal blood clotting is restored with fresh blood and, if necessary, platelet concentrates.

Treatment with fibrinolytic inhibitors, such as aminocaproic acid or aprotinin (Trasylol), could be potentially harmful in that such agents will inhibit plasminogen activation and the clearance of intravascular fibrin deposits. In rare cases, one to two hours after delivery severe postpartum haemorrhage can occur from the placental site. In this postpartum situation, it is possible that enhanced fibrinolysis in the uterus may be contributing, and, if the bleeding cannot be controlled by manual and pharmacological stimulation of myometrial contraction, EACA 4 g intravenously may prove effective in arresting the haemorrhage.

In patients with abruptio placentae, treatment with heparin has been suggested to block the consumption of coagulation factors. In the presence of an intact vascular compartment, this concept would be attractive but in the patient bleeding into the retro-placental space and myometrium due to premature placental detachment, heparin would be likely to aggravate the blood loss or be neutralized by the large amount of platelet factor 4 in circulation. The value of heparin therapy would seem therefore almost impossible to evaluate given the disruption of the coagulation system and the emergency situation which prevails with an acute coagulation disorder.

AMNIOTIC FLUID EMBOLISM

This is the most serious catastrophe which can occur during labour or shortly after delivery. Massive intravascular coagulation occurs and consumption of the clotting factors can be almost total (Bonnar, 1973). The pulmonary vasculature appears to be extensively obstructed with a large amount of platelet-fibrin material. This being so, the rapid transfusion of fluids or blood can precipitate cardiac failure. The aim should be to sustain the circulation until the fibrin deposits are cleared by the active fibrinolytic process present in the pulmonary circulation. The speed of transfusion should be controlled by monitoring the central venous pressure to avoid precipitating cardiac failure. If catastrophic

bleeding from the placental site can be controlled by myometrial contraction, then the most logical treatment is a careful controlled transfusion of fresh blood and heparin administration.

ABORTION

Severe bleeding tendencies and maternal deaths have been reported as a complication of saline-induced abortion (Spivak *et al*, 1972). Changes in the blood coagulation system compatible with diffuse intravascular coagulation have been described by Stander and colleagues (1971) and by van Royen (1974). Hypertonic urea solutions can also precipitate intravascular coagulation (MacKenzie *et al*, 1975). The stimulus would appear to be the placental damage induced by the hypertonic solutions. In patients who suffer from endotoxic shock in association with pregnancy, eg, septic abortion, coagulation failure can arise as a result of diffuse intravascular clotting. In pregnant animals only one exposure to bacterial endotoxin is required to produce the Schwartzman reaction and this may be the result of the diminished fibrinolytic activity in pregnancy which facilitates intravascular fibrin deposition. Where severe bleeding from the uterus is not a problem and evidence of diffuse intravascular coagulation is present, treatment with heparin would seem logical.

Anticoagulant Therapy during Pregnancy

An increasing number of women in the reproductive years are receiving long-term anticoagulant therapy

Fig 6 A comparison of the coagulation factors in the newborn and the mother immediately after birth (15 cases mean + standard error).

because of thromboembolic incidents and heart valve prostheses. Oral anticoagulants during pregnancy are associated with an unusually high fetal mortality. This is not fully explained by the haemorrhagic complications which can arise in the fetus or in the newborn when these drugs are employed in late pregnancy.

Fig 7 Plasma heparin levels in a patient with bilateral iliofemoral thrombosis at the 29th week of pregnancy. Patient used self-administered subcutaneous heparin for four months and breast fed her baby.

In the fetus and newborn, the levels of the vitamin-K-dependent factors II, VII, IX and X are normally low (figure 6). Coumarin derivatives readily cross the placenta and when given to the mother will further deplete the low level of these vitamin-K-dependent factors in the fetus. Haemorrhage which may be fatal or cause non-fatal brain damage is an obvious hazard in the infant during labour or after delivery.

Heparin is the safest anticoagulant to use during pregnancy, and using a regime of self-administered subcutaneous injections we have now treated 60 women for periods of up to six months. In 15 women who received heparin during labour or during caesarean section for prophylaxis or treatment of thromboembolic complications we found no evidence of any heparin in the cord blood with a specific anti-XA assay for heparin. Our experience suggests that long-term treatment with low-dosage, subcutaneous heparin using a self-administration regime, is feasible during pregnancy and the puerperium. A further advantage of this treatment is that it allows breast feeding in the puerperium (figure 7).

For safe and effective therapy, monitoring of the heparin levels in the plasma is required so that adequate heparin is given during the third trimester when neutralization of the heparin takes place due to the intravascular coagulation in the uteroplacental circulation. On average, 7500 to 10 000 units 12-hourly are required in late pregnancy to achieve a heparin level between 0.1 and 0.4 units per ml. We have not encountered any bleeding problems in patients where the heparin level was less than 0.4 units per ml when heparin treatment was continued during labour and delivery or caesarean section. Because of the risk of local bleeding, however, epidural anaesthesia should be avoided in patients receiving heparin prophylaxis (Bonnar *et al*, 1976).

Anacrod (Arvin), the purified fraction of the

venom of the Malayan pit viper, should not be given in pregnancy. In the mouse and rabbit a high incidence of fetal death associated with haemorrhage at the placental site was found (Penn *et al*, 1971).

Streptokinase and urokinase, if administered when delivery is imminent or within one week of childbirth, can produce severe haemorrhage from the uterus. In view of this hazard, streptokinase and urokinase are not recommended save in the exceptional situation where fatal pulmonary embolism appears likely without their use and the risk of severe haemorrhage is accepted.

Conclusion

Pregnancy induces extensive physiological changes in the haemostatic system. Local intravascular coagulation in the uteroplacental circulation is a feature of normal pregnancy which is most likely responsible for the increased production of coagulation factors. The resulting 'hypercoagulability' will also be of benefit to meet the demands on the haemostatic components which inevitably arise at the time of placental separation. These physiological changes produce a vulnerable state for intravascular coagulation and varying degrees of this phenomenon occur in several complications of pregnancy. In preeclampsia, increased intravascular coagulation, as compared to normal pregnancy, is now well documented. In the acute coagulation disorders such as arise with abruptio placentae and amniotic fluid embolism, extensive intravascular coagulation associated with life-threatening haemorrhage can arise. The most effective treatment in such patients is at present the transfusion of fresh blood to maintain the circulating blood volume until the stimulus to intravascular clotting is removed and spontaneous correction takes place.

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