EXPERIENCE OF CALCIPARIN THERAPY IN E.P.H. GESTOSIS

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SUMMARY

The Authors examine their casuistry of EPH gestosis treated with calciparin.

Starting with the premise that, subacute disseminated intravascular coagulation is often en countered in this pathological condition of pregnancy; the haemato-chemical data which are positive in this syndrome, were systematically examined in all the cases of EPH gestosis.

In the positive cases the pregnant women were treated with calciparin by subcutaneous route. Although the number of cases was limited, the success obtained encourages the continuation of this therapy.

No particular side-effects noxious to the mother or the foetus were encountered.

Many conditions in obstetric pathology are capable of giving rise to a syndrome of disseminated intravascular coagulation. Thys syndrome is characterized by increased coagulation within the small vessels, an increase which is brought about by the presence in the circulation of anomalous activators of the processes of coagulation. These phenomena start a diffuse coagulative process with platelet aggregation and thrombocytopenia, indicating the consumption of coagulation factors and the formation of thrombin, which transforms the circulating fibrinogen into clots of fibrin.

In this way thrombi are formed in the microcirculation of all the organs, and their presence activates the local fibrinolytic processes that the lead to the formation of plasmin (fibrinolysin), which breaks down the thrombi, by the enzimatic route, into products of the solubre fibrins (Table 1).

There is thus a dual biochemical foundation for disseminated intravascular coagulation: pathological coagulation of the circulating blood and a local hyperfibrinolysis reaction in the microcirculation. All the formed fibrin is removed by secondary fibrinolysis, representing the endothelial response, via the liberation of an activator of plasminogen. The fibrinolytic response may be excessive and this, in addition to fibrinolysis, brings about lysis of the fibrinogen. This consumption of fibrinogen by two different means, is the cause of the rapid depletion of fibrinogen present in the circulation (Table 2). Both fibrinolysis and fibrinogenolysis then lead to the formation of FDP (fibrinogen degradation products). It should not be forgotten that the appearance of disseminated intravascular coagulation is encouraged by blocking the reticuloendothelial system, which is notoriously depressed during pregnancy.

The reticuloendothelial system has the task of removing from the circulation the fibrin and other mycelial substances, preventing them from giving rise to the formation of further clots, in addition, the

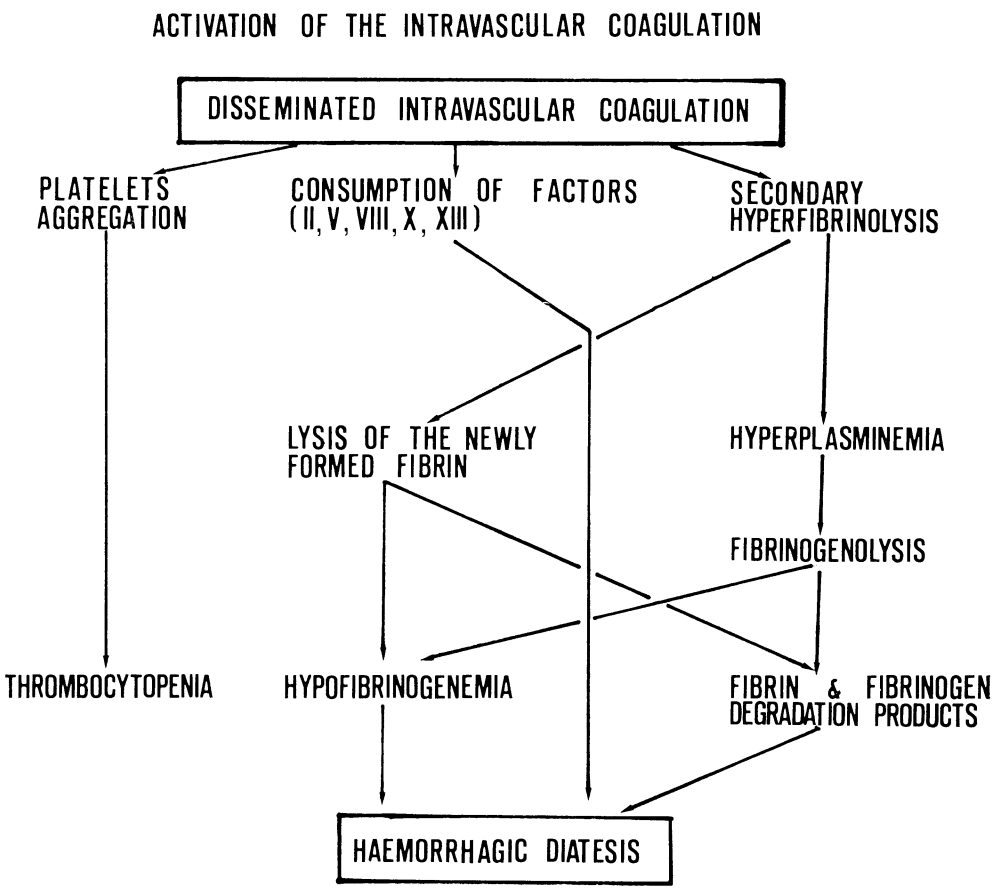

Table 1. — Pathogenesis of the haemorrhagic diatesis in course of D.I.C.

RES also removes thromboplastin and precoagulant substances from the circulation.

It is known that the uterus is a very rich source of plasminogen activators. The degradation products of fibrin, in fact, as was shown by the work of some Authors ([3]), show increased blood concentration in women during menstruation, especially in those who have a metrorrhagic type of flow. It is also known that the extensive availability of thromboplastin from the placental tissue seems, according to the best accredited theory, to be the basis of the pathological phenomena of coagulation.

Therefore, various conditions in obstetric pathology that produce lesions at placental or "uterine" level may cause the onset of disseminated intravascular coagulation (Table 3) ([2, 4, 9, 10]). While the acute forms run a rapid, severe and dramatic course, characterized by signs of severe blood coagulation and thus are not difficult to recognize and diagnose, the subacute or chronic forms, in which there are no symptoms related to the blood, present the greatest diagnostic difficulties. It is precisely in these forms that early diagnosis and controlled therapy may preserve some organs, the kidneys in particular, in

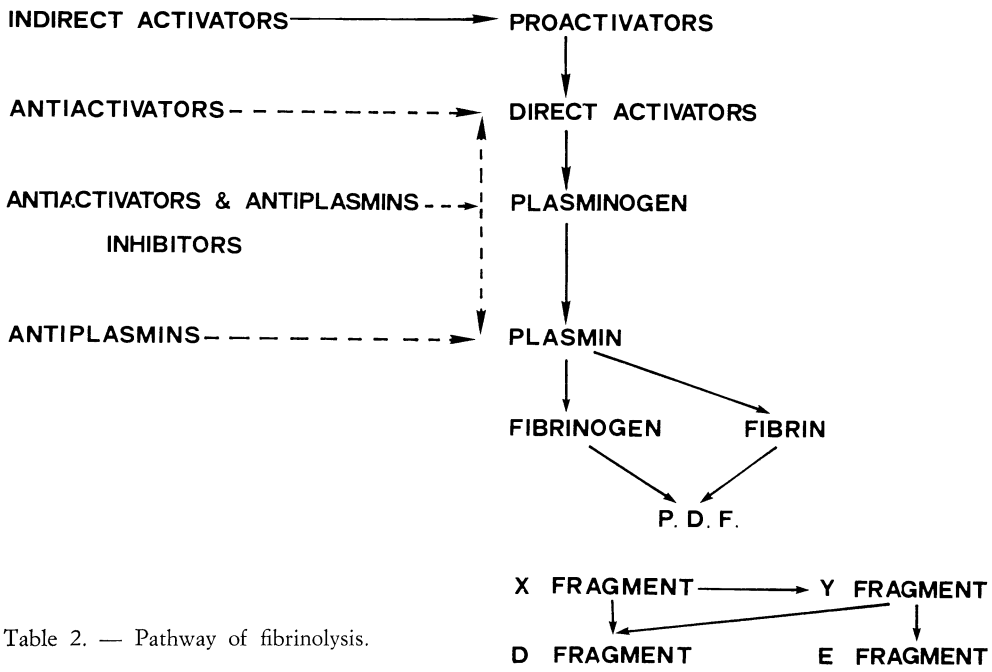

Table 2. — Pathway of fibrinolysis.

which the lesions, once considered irreversible, most often lead to the death of the patient. Among these chronic forms of disseminated intravascular coagulation has also been recognized EPH gestosis, both by us and other Authors ([2, 4, 9, 10]).

This morbid condition is characterized by proteinuria, oedema and hypertension. It is now often termed "imminent eclampsia". If it becomes more serious and is associated with a diminution of renal function or convulsions, we then speak of "eclampsia of pregnancy".

In the kidney, in toxaemia of pregnancy, the glomeruli are the site of greatest involvement. Ultra-structural tests, and work with fluorescent antibodies, have in fact shown that the protein deposits in the glomeruli (electro-dense protein deposits between the endothelium and the basal membrane of the glomerulus, and within the mesangium) are composed substantially of profibrin ([2, 5, 8]). It seems, in fact, that in consequence of activation of the mechanism of coagulation, fibrinogen that is only partially polymerized appears in the circulation; this is thus intrapolated and filtered from the glomerulus, with consequent increase in the glomerular permeability and therefore proteinuria. These renal lesions seem to be secondary to disseminated intravascular coagulation due, according to some Authors, to the action

Table 3. — *Diseases which can complicated with D.I.C.*

Amniotic fluid embolism
Placenta's premature separation
Missed intrauterine fetal dead
Vescicular mola
E.P.H. gestosis
Septic abortion
Amnionitis

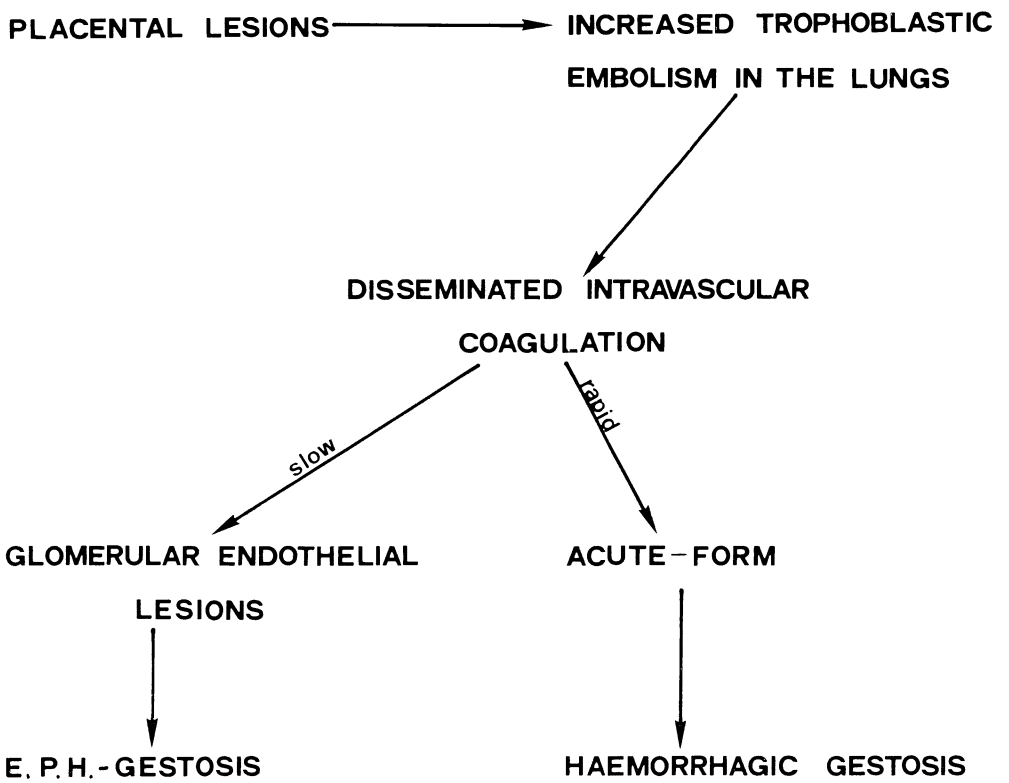

Table 4.

of trophoblastic micro-emboli. These emboli (notoriously possessing a high thromboplastin activity) are blocked at the level of the capillaries of the pulmonary circulation, where they undergo a process of lysis which gives rise to the liberation and diffusion into the systemic circulation of the thromboplastin factors contained in them (Table 4).

The convulsive manifestations of eclampsia seem also to be a consequence of the phenomena of disseminated intravascular coagulation. This is acutely confirmed in the cerebral circulation with the formation of micro-thrombi of fibrin and platelets associated with signs of vessels crammed with blood.

Lesions secondary to the formation of fibrin micro-thrombi may also be demonstrated in the liver, spleen and suprarenals. Starting from the presupposition that in this disease, one of the fundamental pathogenetic factors consists of these alterations in the microcirculation, various Authors have suggested heparin treatment, and have carried it out with success. The purpose of this therapy would be to arrest the tendency towards disseminated intravascular coagulation, and thus to interrupt the vicious circle typical of EPH gestosis. Consequently those organs, the kidney in particular, in which alterations would aggravate the prognosis of this morbid conditions, would be preserved.

Table 5.

Case	Name	Age	Gestational age	Clinical syndrome	Maternal outcome	Fetal outcome	Delivery
1st	P. C.	26	38 weeks	E.P.H. gestosis	Good	Alive/Stillborn 1950 g	Cesarean section
2nd	P. M. C.	38	37 weeks	E.P.H. gestosis	Good	Alive/Stillborn 3050 g	Cesarean section
3rd	D. C. A.	40	39 weeks	E.P.H. gestosis	Good	Intrauterine fetal death	Spontaneous
4th	C. F.	35	37 weeks	E.P.H. gestosis	Good	Alive/Stillborn 2950 g	Cesarean section
5th	M .G.	26	39 weeks	E.P.H. gestosis	Good	Alive/Stillborn 3100 g	Spontaneous
6th	P. C.	39	32 weeks	D.P.N.I.	Good	Intrauterine fetal death	Postpartum hysterectomy
7th	P. A.	22	16 weeks	Haemor. gestosis + Vescicular mola	Dead	—	Total hysterectomy bilateral ooforectomy

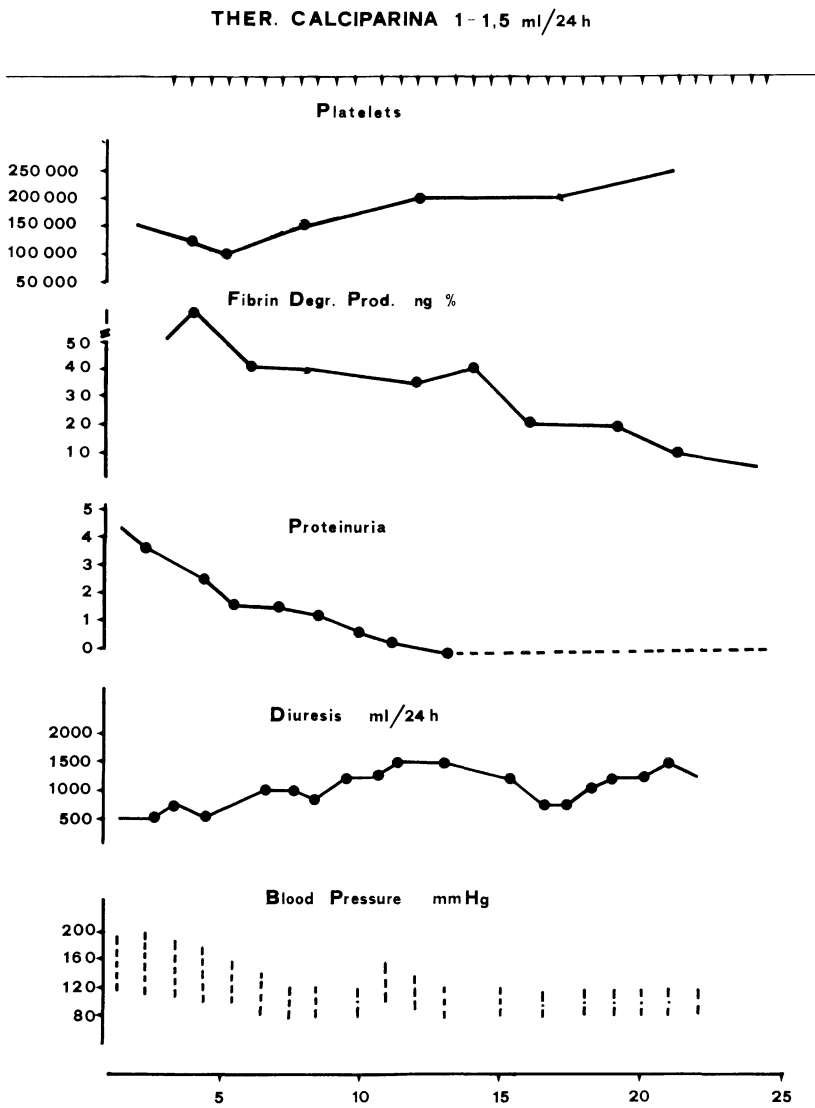

Table 9. — P. C.: Age 26. 1st pregnancy. C. S. at the 36th week of gestation. E.P.H. gestosis, male neonate 1950 g alive/stillborn.

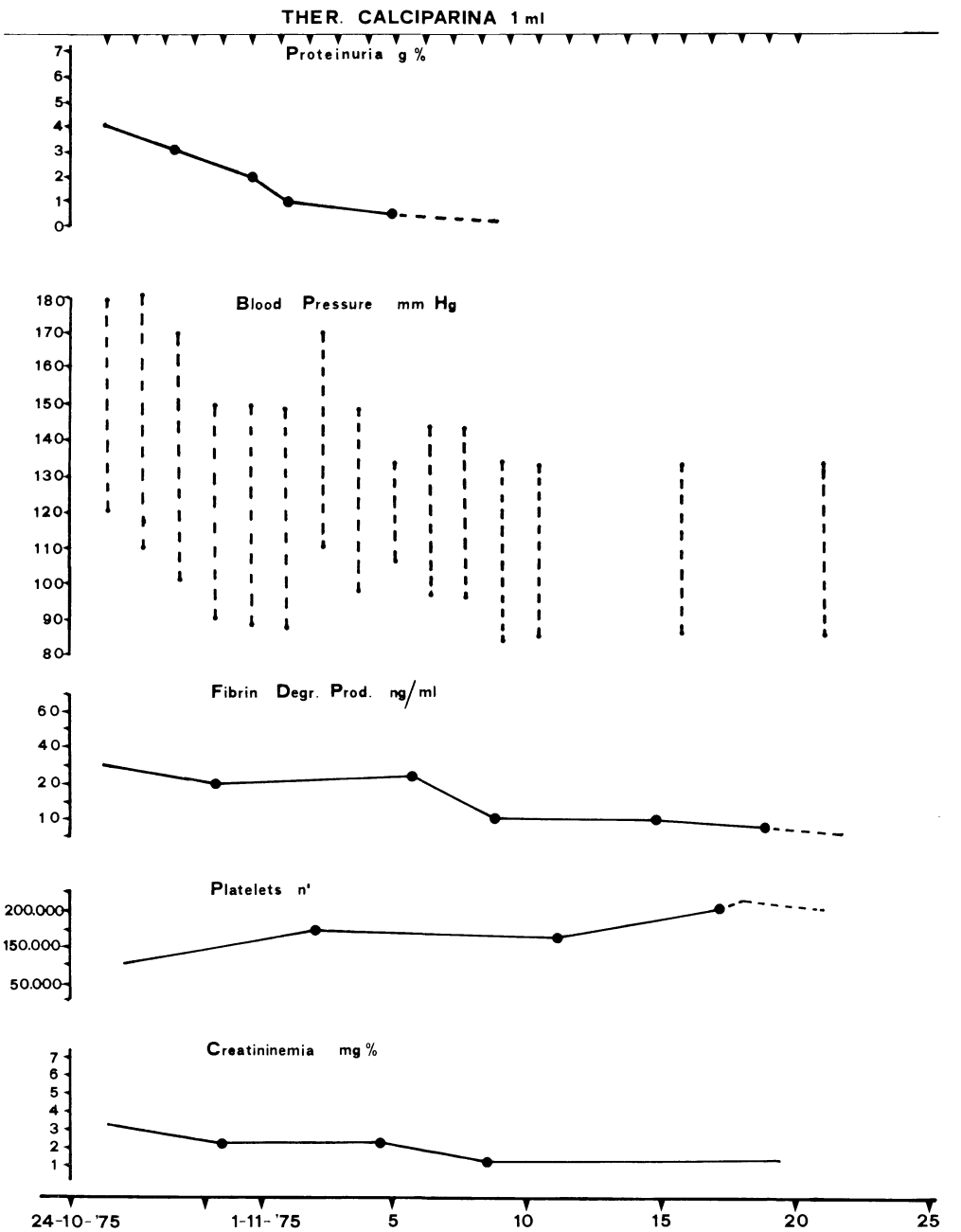

Table 7. — P. M. G.: Age 38. 1st pregnancy. E.P.H. Gestosis. Cesarean section at the 37th week of gestation. Female neonate.

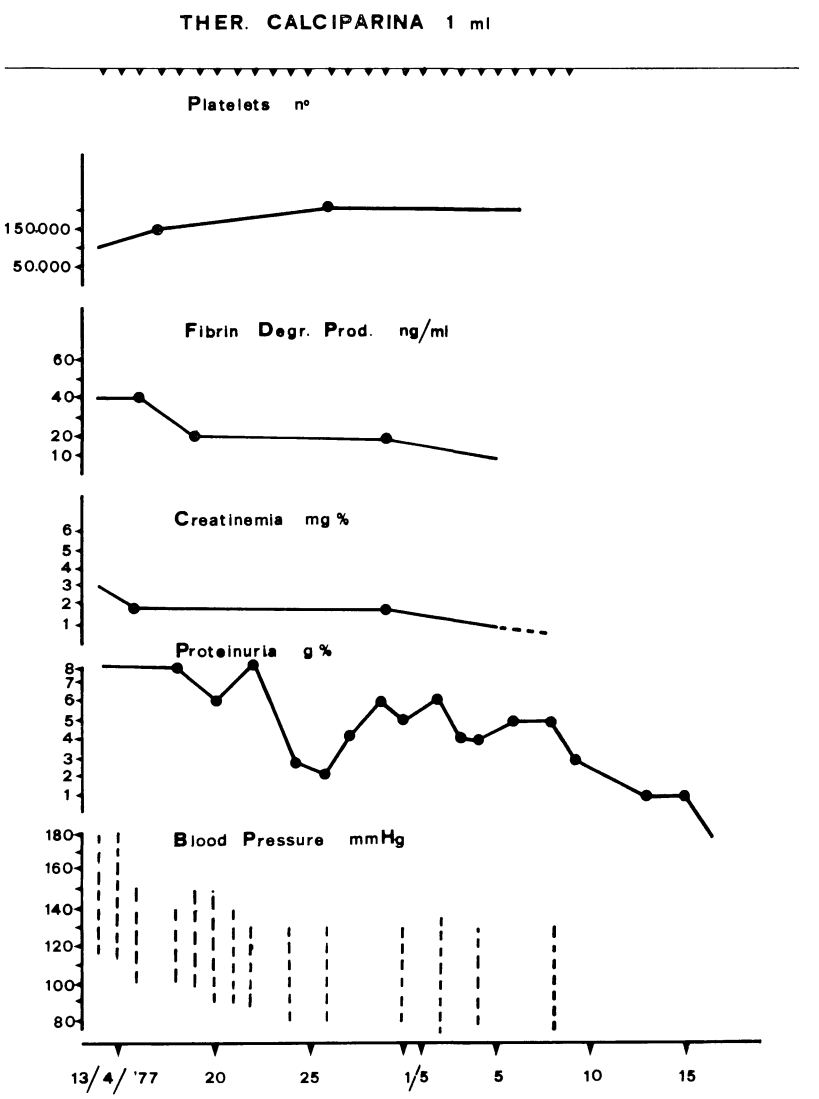

Table 8. — D. C. A.: Age 40. 1st pregnancy. E.P.H. gestosis. Spontaneous delivery at the 39th week of gestation. Female fetus dead. Weight 1750 g.

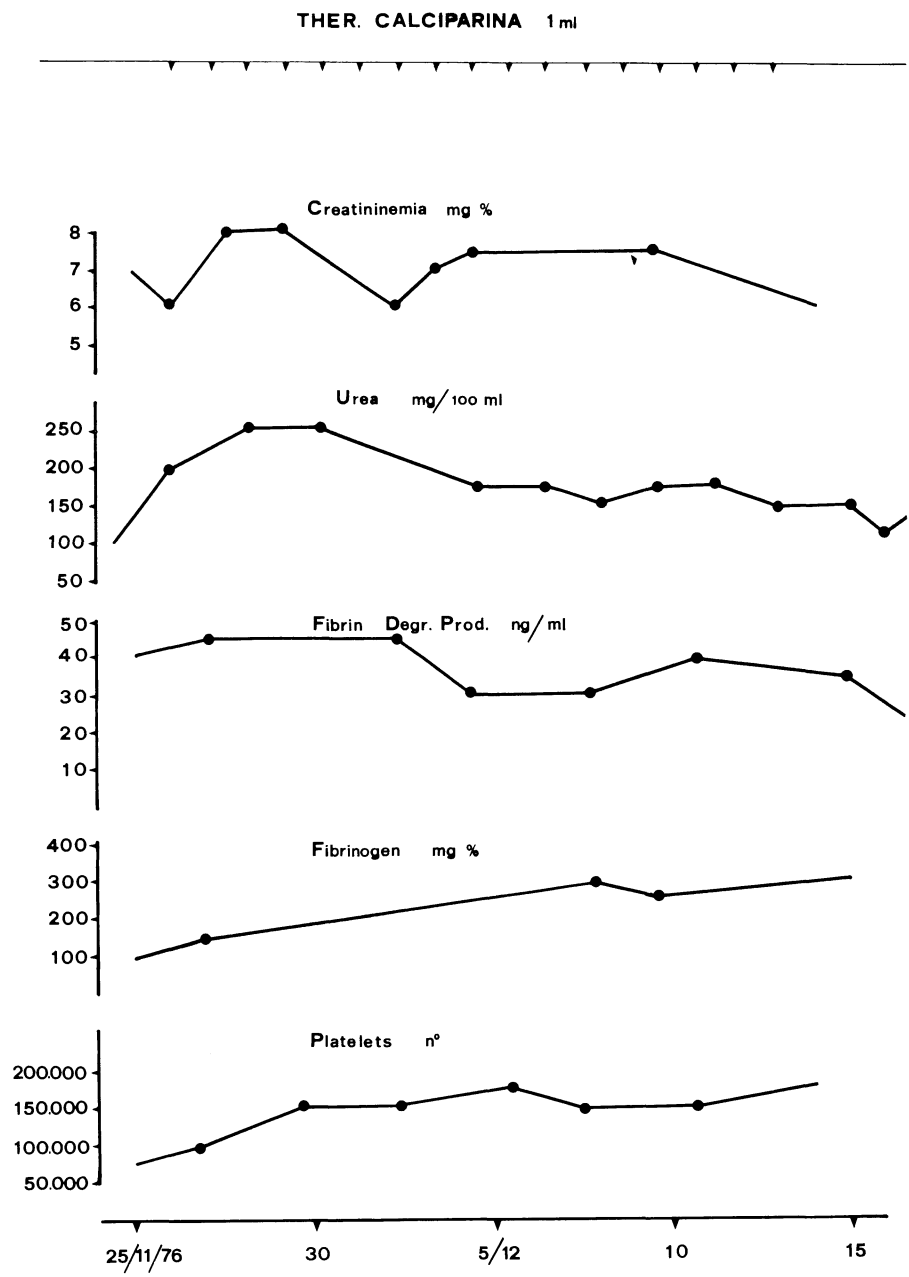

Table 6. — P. C.: Age 39. 3rd pregnancy. Placenta's premature separation at the 32nd week of gestation. Cesarean section. Male neonate 1800 g.

MATERIAL AND METHODS

On the basis of our previous experience (1974), we turned our attention, in the cases of EPH gestosis seen in our Clinic, to the phenomena of intravascular coagulation. The diagnosis of disseminated intravascular coagulation was made after checking the following parameters:

1) number of platelets
2) fibrinogen level
3) FDP level.

In all the cases of EPH gestosis in which there was thrombocytopenia, hypofibrinogenaemia and, most of all, the presence of FDP in the blood, we initiated treatment with heparin, in addition to the usual sedatives (phenobarbital), diuretics (furosemide) and dietetic therapy.

Our preference was for calciparin, since this can be given subcutaneously (in the peri-umbilical region) every 12 hours, so that absorption and the blood level remain constant, unlike heparin, which is administered rapidly during the first period and slowly during the second, i.e. intravenously every 6 hours (furthermore this characteristic did make it possible to carry out treatment at the patient's home).

The initial dose was 1 ml of calciparin twice a day, with some modifications (more or less) following the values of Howell's time dosed daily, in order to have a pharmacological dose not noxious on coagulation.

Calciparin therapy was suspended, whenever possible, 24 hours before delivery and started again 72 hours after birth.

RESULTS

The cases in which we gave calciparin therapy are summarized in table 5.

These were five cases of imminent eclampsia, one case of placenta premature separation and one case of hydatidiform mole. These patients presented not only the clinical symptoms of gestosis (proteinuria, hypertension, oedema), but also thrombocytopenia, hypofibrinogenaemia, and a high level of degradation products of fibrin in the blood. As can be seen from tables 6, 7, 8, 9, the blood coagulation, as well as the arterial pressure and proteinuria, responded satisfactorily to calciparin therapy.

For us the most significant finding was the return to normal of the clinical parameters (arterial pressure, proteinuria, oedema) as well as the improvement in the subjective symptoms, with consequent return to normal of blood coagulation parameters, and finally, the disappearance, of signs of disseminated intravascular coagulation.

DISCUSSION AND CONCLUSIONS

The treatment of EPH gestosis has always been a serious problem, due to the high maternal and foetal mortality rate. While in the past there was a tendency to regard this morbid condition as irreversible in the sense of complete anatomical and functional recovery of the various organs involved, more recent studies have demonstrated that at long term, the organs and systems involved, do return to complete normality.

Starting from this supposition and from the fact that a subacute syndrome due to coagulation disease and consumption may be demonstrable in this condition, calciparin therapy seems to be the optimal therapeutic solution in these cases.

Our experience on calciparin therapy in EPH gestosis, when administered subcutaneously, is still limited. But on the basis of the good results we have obtained, it seems nevertheless to be an effective therapy in resolving the symptomatological and clinical picture. Side-effects are infrequent, while the route of administration is particularly advantageous.

The dose used was 1 ml s.c. every 12 hours (1 ml corresponds to 25,000 units). When administered subcutaneously, the effect of calciparin lasts for 8 to 12 hours; thus, two daily administrations give constant and efficient heparinaemia.

According to some Authors (1968), effective heparinaemia appears after only 15 minutes, and any overdosage can be corrected by administering protamine sulphate. No changes in the plasma concentra-

tion of Ca, Mg and sodium derivatives was found as a result of this therapy.

According to most recent theories, one of the fundamental pathogenetic factors in EPH gestosis is subacute coagulation disease; for this reason calciparin could be the drug of choice. In our subjects treated in this way, we always found, after the blood coagulation had returned to normal, a marked, improvement in the anatomical and clinical parameters.

The interesting finding, besides the immediate result (maternal and neonatal wellbeing), was the complete clinical and functional cure of our patients, as proved by long-term follow-up.

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