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Outpatient management of placental insufficiency with heparin

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It has been demonstrated that continuous administration of heparin during pregnancy results in an improvement of placental insufficiency [1, 2, 3, 4, 5]. This is based on the assumption that the nutritional insufficiency is caused maintained by a disturbance in the microcirculation due to platelet aggregation and fibrin deposits. By inhibiting these coagulation processes the disturbances of metabolic exchange might be alleviated. Generally, the method has been to admit patients to the hospital and save for some exceptions [1] to administer heparin by constant infusion (20–40,000 IU/day). While this method is rational it has the great disadvantage of requiring long-term hospitalization which even highly motivated patients are often unable to accept. Based on the experiences with the post-operative prophylaxis of thrombosis with heparin in intermittent low doses subcutaneously we have attempted to treat cases of placental insufficiency in this fashion as well. We expected these results to be less successful than those with continuous infusions with heparin; the method nevertheless is more practical.

1 Material and methods

Thirteen pregnant women with suspected placental insufficiency were admitted between the 29th and 37th week of gestation. Depending upon their weight they received 5000 units of heparin subcutaneous injection in 8–12 hour intervals. The patients or their husbands learned the injection technique and the further treatment was carried out at home similar to that in diabetics provided that the patient was ready, able and willing. The therapy was discontinued at term or when the desired therapeutic objective had been obtained.
The placental insufficiency was followed by ultrasonography, daily estriol excretion (radio-immunoassay) as well as serum estriol and HPL determinations.
Coagulation studies were not carried out.

2 Results

Tab. I summarizes onset and duration of the heparinization and other relevant clinical data. One infant (case 10) died soon after birth because of renal agenesis. The placenta had marked signs of severe insufficiency. Another infant (case 12) died in utero from severe placental insufficiency during the treatment with heparin.
Table 2 correlates the birth weight and weight: length ratio with the standards of NICKL [6]. In retrospect case 2 was probably not placental insufficiency even though the urinary estriol excretion was consistently at 5 mg/24 hours. Possibly case 8 in retrospect was also not a placental insufficiency, however, the patient's history had indicated one.
The assessment of the therapeutic success was based on the growth increment of the biparietal diameter as well as the increased estriol excretion (see also Figs. 1 and 2). In six cases the effect of the treatment was satisfactory, in three cases moderate, and in one case the treatment failed

Tab. I. Outpatient heparinization – Case

Case	Heparinization Onset (week)	Heparinization Duration (weeks)	Gestational Age (weeks)	Infant Measurements length weight	Notes
1	36	2	38	49/2750	placenta: fibrin deposits
2	35	4	39	51/3150	
3	30	7	42	54/3300	
4	32	8	40	53/2950	placenta: extensive ischemic infarcts, calcium deposits
5	29	7	38	48/2500	smoker
6	30	8	38	52/2650	
7	32	6	38	51/2900	placenta: fibrosis of primary villi, focal calcium deposits, intravillous fibrin deposits
8	35	2	40	54/3600	suspect history
9	37	3	40	55/3150	
10	30	9	39	48/2500	neonatal death: renal agenesis, multiple anomalies placenta: ischemic infarcts, fibrin deposits
11	30	6	42	54/3500	placenta: infarcts
12	32	3	35	40/1150	intrauterine death: severe placental insufficiency placenta: weight 150 g, many infarcts
13	36	3	40	52/2800	

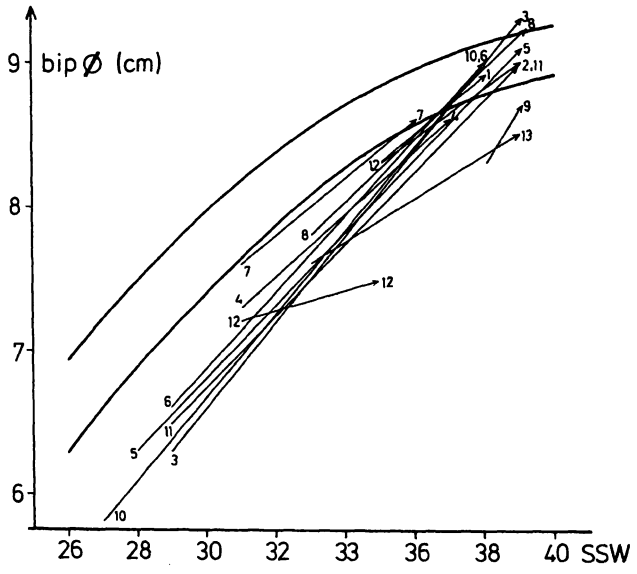

Fig. 1. Ultrasound measurements during treatment of placental insufficiency with low dose heparin. Values before and after onset of treatment are depicted. Note the pathological original value (arrow) and the subsequent steeper than expected increase of the biparietal diameter.
bip ϕ: biparietal diameter (cm)
ssw : weeks of gestation

completely. Case 10 cannot be judged because of the existing severe malformation. As demonstrated in Figs. 2 and 3 several cases have an above average increase of estriol excretion and HPL serum levels, however, the growth of the biparietal diameter (Fig. 1) demonstrates much more clearly the effect of the heparin treatment. The serum estriol values which have not been depicted allow only barely the recognition of the efficacy of the treatment. The normal variations of the values in these three hormonal assays are too large for a unquivocal assessment of the therapeutic effect.

Fig. 4 illustrates one case. With normal ultrasound findings initially, in mid-pregnancy growth retardation occurs which was corrected after initiation of the ambulatory heparin treatment. The urinary estriol excretion and serum HPL values increase slightly above the normal after the onset, however, no pre-treatment values were available.

3 Discussion

The treatment of placental insufficiency with heparin was based on the thought that a pathologically increased fibrin deposition in the intervillous space causes a circulatory disturbance and inhibits diffusion. This leads to the clinical picture of fetal growth retardation. While heparinization may be a reasonable suggestion, its efficacy has

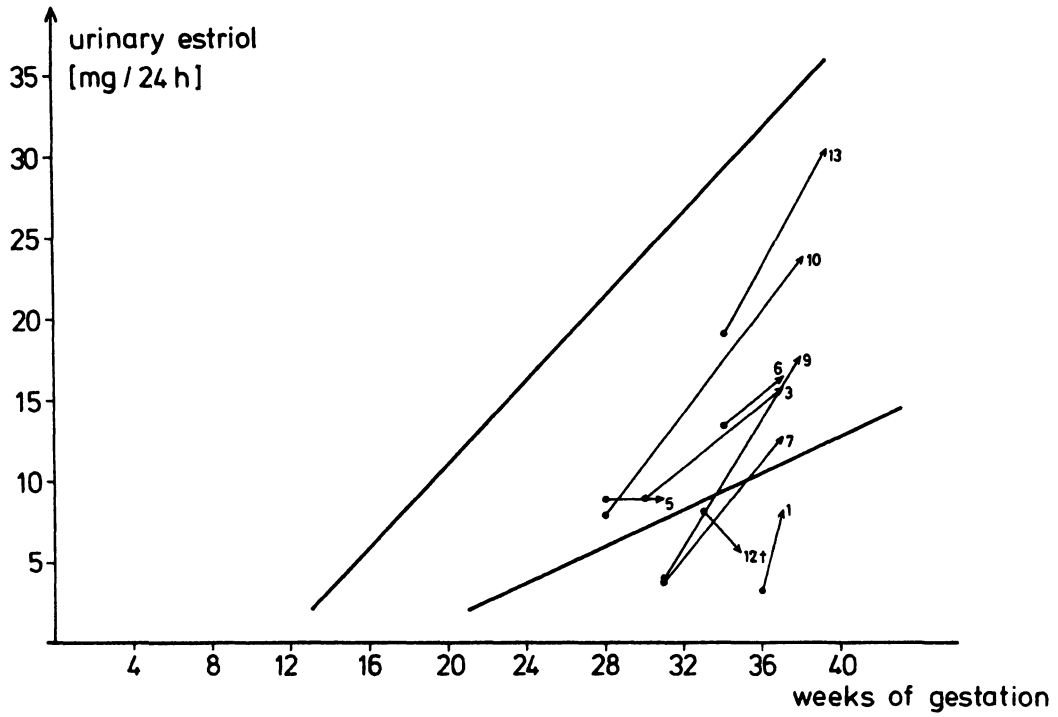

Fig. 2. 24 hour urinary estriol excretion in placental insufficiency during outpatient heparinization. Depicted are values before treatment and the last values during treatment.

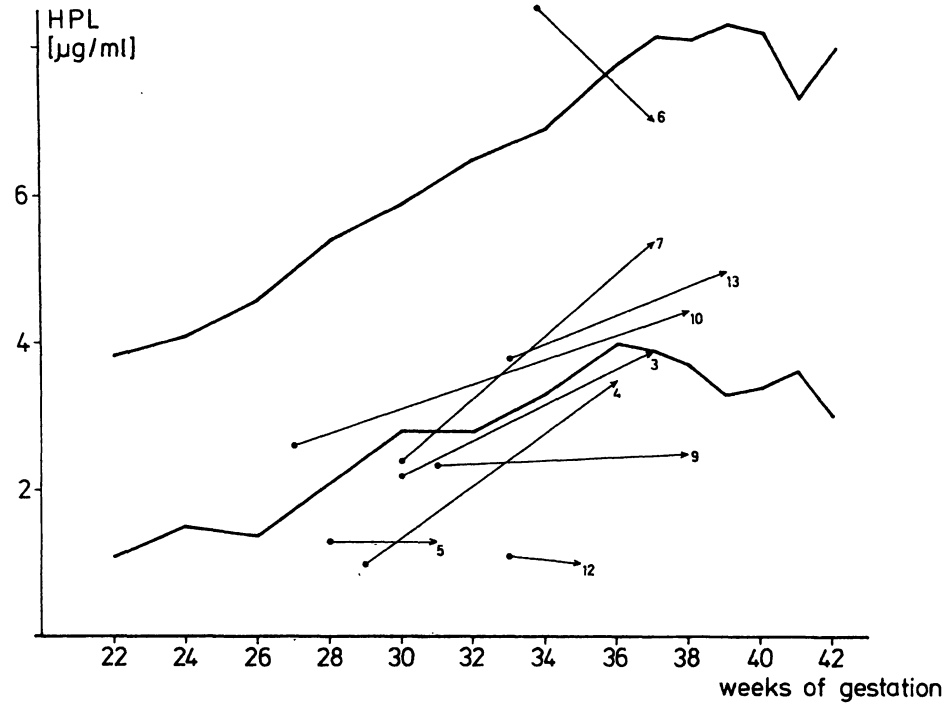

Fig. 3. HPL level in cases of placental insufficiency during outpatient heparinization. Depicted are values before treatment and the last values during treatment.

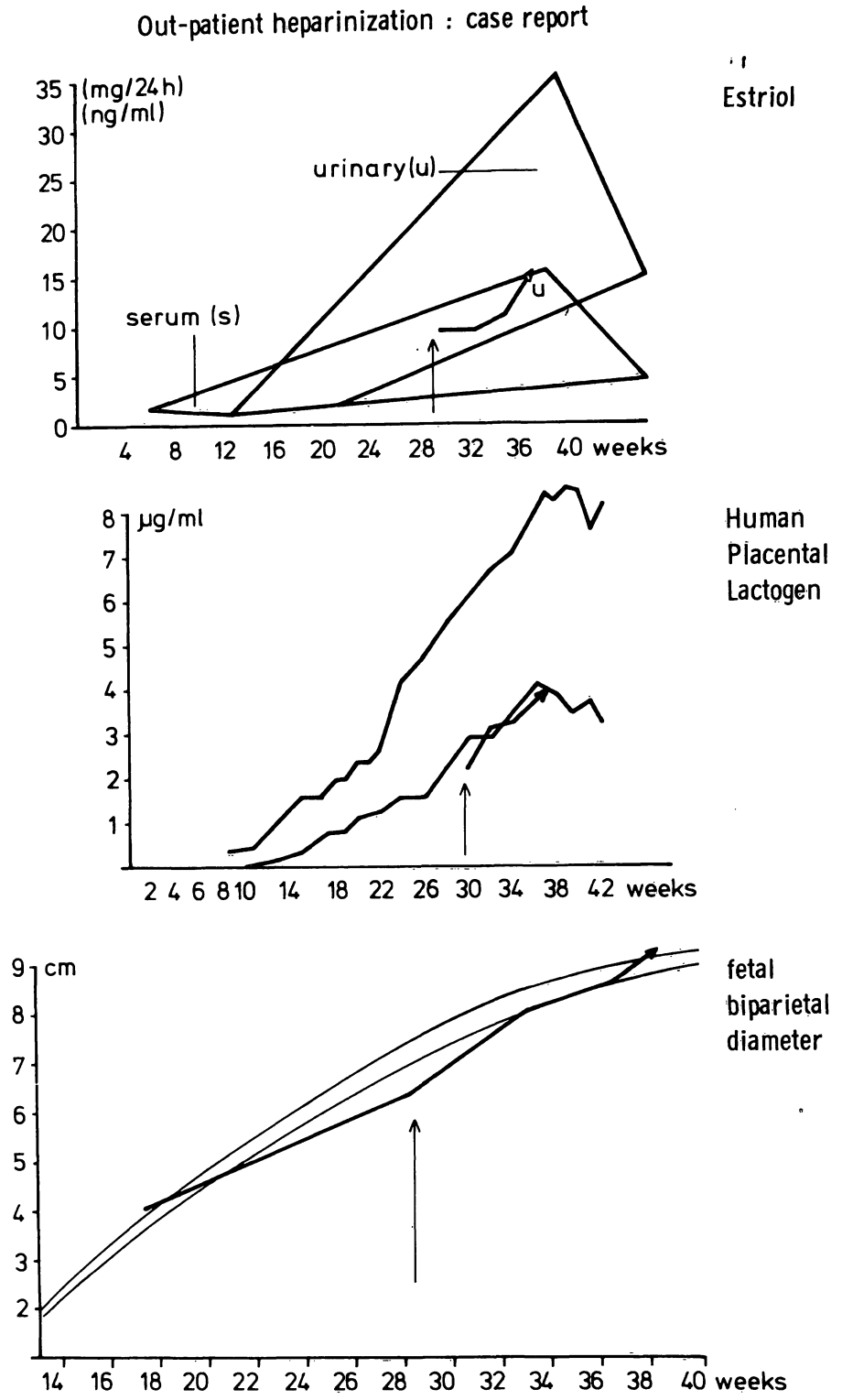

Fig. 4. Illustration of a case (case 5) of placental insufficiency. The arrow marks the onset of the outpatient heparin therapy.

not been proven for several reasons. The intrauterine diagnosis of a placental deficiency is very difficult. While there are several methods available, errors in measurement and biological variability are relatively large. On the other hand, the therapeutic effort of a continuous heparinization in the hospital with bed rest is so high that a standardized therapy with larger groups of patients has not been done. The lack of comparable cases even in large hospitals is another reason for the lack of

controlled studies. Lastly, the efficacy of heparinization is limited in that a growth retardation or decreased hormonal levels during the existing placental insufficiency has already occurred. Since existing fibrin deposits cannot be dissolved, at best only further deterioration can be prevented. Other factors of placental insufficiency remain uninfluenced, e.g. disturbances in villous maturation, decreased vascularization and other functional pathological factors. LUDWIG [5] demonstrated unequivocally pathologic fibrinization of the utero-placental vascular bed. Thus, increased fibrin deposits may at least in part, participate in the clinical presentation of placental insufficiency.

Experiences with continuous heparin treatment [1, 2, 3, 4, 5] thus far have been equivocal. In selected cases, however, therapy seems to be promising. The principal disadvantage is the continuous infusion requiring hospitalization. Therefore, the initiation of treatment is often delayed and limited. Ambulatory treatment as chosen by us based on the good experiences with the subcutaneous post-operative prophylaxis for thrombosis allows the generous prophylatic use of low dose heparinization when placental insufficiency is suspected. The disadvangage undoubtedly is the possibility for lesser efficacy because of the low doses.

In two of our 13 cases a placental insufficiency could retrospectively be excluded. In one case therapy failed because it was started too late and the irreparable placental insufficiency could not be abated. The fetus died in utero during the treatment. In another case of severe placental insufficiency, the infant died post-partum with renal agenesis. Therefore, this case was excluded from the evaluation. The remaining nine cases were predominately successful. In particular the longitudinal growth which correlates well with the increase of the biparietal diameter was stimulated while the weight increase in relation to the lon-

Tab. II. Results of heparin treatment of placental insufficiency: comparison of birth weight and weight: length ratio with the standard curves of NICKL.

Case	Birth Weight Percentile	Weight/ Length Ratio Percentile	Growth of biparietal before Heparin	Growth of biparietal after Heparin	Success +	Success ±	Success −	Comment
1	< 10	< 10	0.10	0.25		x		E_3 3.3 → 8.4 Therapy too late, too short
2	< 50	< 25	0.15	0.17				Retrospectively no placental insufficiency E_3 constant 5.0
3	< 50	< 50	0.20	0.22	x			E_3 9.0 → 16.0
4	< 25	< 3	0.22	0.26	x			
5	< 10	= 3	(6.3 28	0.24	x			
6	< 10	< 3	0.13	0.29	x			
7	< 25	< 25	0.25	0.15	x			E_3 1.0/3.9 → 13.9
8	> 50	> 50	0.20	0.22				Retrospectively no placental insufficiency suspect history
9	< 25	< 10	0.06	0.20	x			E_3 4.0 → 18.0
10	< 3	< 3	0.23	0.31				E_3 8.0 → 24.0 malformation
11	> 50	< 50	0.23	0.22		x		
12	≪ 3	≪ 3	0.26	0.10			x	too late, too short E_3 constant < 8.0
13	< 10	< 3	0.20	0.12		x		too late, too short E_3 17.2 → 30.6

gitudinal growth remained behind. Consequently, the weight: length ratio in many cases is at a lower percentile than the birth weight (Tab. II). In some cases [1, 12, 13] therapy appears to have been initiated too late and the duration was too short.

This investigation has to be considered as a pilot study which would be collaborated with larger numbers of patients. Especially we can not yet make any statements about indications, the limits of the treatment or the possible usefulness of true prophylaxis. Thus far we have used heparinization only in patients with pathological ultrasonographic and hormone findings, i.e. only after some impairment has already occurred. This would be irreversible if fibrin deposits have already occurred. Therefore, the hypothesis of true prophylaxis would have to be tested in cases of placental insufficiency in preceding pregnancies. Lastly, it is not clear whether the dose used in this study is sufficient considering the already present thromboplastin activity with existing placental insufficiency.

A prerequisite for the practical use of outpatient therapy is a practical dose form. Objectives are the smallest possible injection volumes, a reliable standardization, and packaging in a one-way syringe or 5000 unit ampule in order to avoid dosage errors.

In summary, we believe that intermittent heparinization of outpatients for placental insufficiency has theoretical advantages. This must be based on an early diagnosis with ultrasound measurements and hormone analysis. The therapy has to be initiated even in suspected cases and it can be carried out in our experience by the ambulatory patient herself or members of her family. This mode of treatment requires adequate planning and cooperation by the patient. For severe cases of placental insufficiency outpatient heparinization is probably inadequate and hospital admission with bed rest and continuous heparinization in higher doses is necessary.

With these doses coagulation studies are not necessary. These heparin doses which are below the threshold interfer merely in the early phase or coagulation. By inhibition of activated factors IX, X, XI they delay the release of thromboplastin. The normal coagulation status of the blood is quickly re-established so that all other coagulation values are remaining largely in the normal range [7].

Summary

Treatment of placental insufficiency with heparin is based on the theory that the nutritive insufficiency is maintained by platelet aggregation and fibrin deposits on the villi and that it might be abated by inhibiting these coagulation processes. In earlier studies about the efficacy of heparin treatments patients have been hospitalized and treated with continuous infusion of heparin. The results were generally satisfactory. The disadvantage of this mode of treatment is undoubtedly the necessity for hospitalization and continued infusion. This has prevented larger numbers of patients from being studied and therapy is often begun late. Based on the good experiences with post-operative thrombosis prophylaxis by low dose heparinization we have attempted to treat placental insufficiency with the same doses in outpatients. **Patients were admitted initially when placental insufficiency was suspected and depending on their weight received two to three times daily 5000 units of heparin subcutaneously.** After being trained in the injection technique treatment was continued by the patient or her husband at home.
The diagnosis of placental insufficiency and the further course was monitored with ultrasonography, urinary estriol excretion and the determination of HPL and estriol in the serum. The study comprises 13 patients.
The successful treatment was best indicated in the increasing growth of the biparietal diameter which was noticable above the expected level. Similarly the 24 hour urinary estriol excretion increased at times more than was expected from the course of the pregnancy. In contrast the monitoring with serum estriol and serum HPL were less satisfactory. Our results were fairly encouraging. In some cases therapy began too late, lasted too briefly or remained unsuccessful. A prerequisite for a successful treatment with ambulatory low dose heparinization is the early or even prophylactic use of therapy in suspected cases of placental insufficiency and the consistent long-term treatment. In severe cases of placental insufficiency the patient should be hospitalized and the heparin given by continuous infusion in higher doses.

On the other hand one should not have too high expectations from this mode of treatment since undoubtedly the inhibition of placental coagulation processes represent only a partial solution of the problem of placental insufficiency.

Additional important factors for this therapy are the understanding and cooperation of the patient as well as the availability of suitable heparin dose forms from the pharmaceutical industry. A small injection volume with a

standardized content of 5000 units in a one-way syringe or one dose ampule is desirable.

Keywords: Heparinization, placental insufficiency.

Zusammenfassung

Ambulante Heparinisierung bei Placentainsuffizienz

Die Behandlung der Placentainsuffizienz mit Heparin gründet sich auf die Vorstellung, daß die nutritive Insuffizienz durch Thrombozytenaggregationen und Fibrinablagerungen an den Zotten unterhalten werde und durch eine Hemmung dieser Gerinnungsabläufe behoben werden könnte. In früheren Untersuchungen über die Effektivität der Heparinbehandlung wurden die Patientinnen hospitalisiert und mit Dauerinfusionen von heparinhaltigen Lösungen behandelt. Die mitgeteilten Erfolge waren im allgemeinen befriedigend. Der größte Nachteil dieser Behandlungsform ist zweifellos die Notwendigkeit der Krankenhausaufnahme und Infusionsdauerbehandlung. Durch diesen überhöhten therapeutischen Aufwand werden größere Untersuchungsreihen verhindert und die Therapie im allgemeinen zu spät eingesetzt.

Ausgehend von den guten Erfahrungen mit der postoperativen Thromboseprophylaxe durch low-dose-Heparinisierung haben wir versucht, auch die Placentainsuffizienz in gleicher Dosierung und ambulant zu behandeln. **Die Patientin wurde unter dem Verdacht auf Placentainsuffizienz stationär aufgenommen und erhielt je nach Körpergewicht 2- bis 3-mal täglich 5000 IE Heparin subcutan injiziert.** Nach Erlernen dieser Injektionstechnik durch die Patientin oder den Ehemann wurde die Behandlung ambulant fortgeführt.

Zur Diagnose der Placentainsuffizienz und zur weiteren Verlaufskontrolle dienten die Ultraschall-Kephalometrie, die Bestimmung der Östriolausscheidung im 24-Stundenurin und die Bestimmung von HPL und Östriol im Serum. Es werden insgesamt 13 Patientinnen vorgestellt.

Die Erfolge der Therapie zeigten sich am besten in der zunehmenden Wachstumstendenz des biparietalen Durchmessers, die deutlich über dem zu erwartenden Niveau lag. Auch die Östriolausscheidung im 24-Stundenurin stieg mitunter stärker an als dem Schwangerschaftsverlauf normalerweise entspricht. Demgegenüber waren Verlaufsbeobachtungen von Serum-Östriol und Serum-HPL weniger befriedigend. Insgesamt können unsere Therapieerfolge als relativ ermutigend angesehen werden. In einigen Fällen setzte die Therapie zu spät ein, war von zu kurzer Dauer oder blieb erfolglos. Voraussetzung für eine effekte Behandlung in ambulanter low-dose-Heparinisierung sind der frühe und auch prophylaktische Einsatz der Therapie bei Verdachtsfällen und die konsequente langandauernde Durchführung. Bei schweren Fällen von Placentainsuffizienz sollte die Hospitalisierung und Dauerinfusionsbehandlung in höherer Dosierung angestrebt werden.

Zur Dämpfung überhöhter Erwartungen muß weiterhin festgestellt werden, daß die Hemmung der placentaren Gerinnungsabläufe zweifellos nur eine Teillösung des Problems Placentainsuffizienz darstellen kann.

Weitere wichtige Voraussetzungen zur Durchführung dieser Therapieform sind die Einsicht und die Bereitschaft der Patientin zur Mitarbeit sowie die Bereitstellung von geeigneten und fehlervermeidenden Heparin-Abpackungen der Industrie. Anzustreben sind kleine Injektionsmengen mit standardisiertem Inhalt von 5000 IE Heparin in Einmalspritze oder Einzelampulle.

Nach unseren Erfahrungen und Angaben der Literatur sind gerinnungsphysiologische Untersuchungen während der Therapie im allgemeinen nicht erforderlich.

Schlüsselwörter: Heparinisierung, Placentainsuffizienz.

Résumé

Traitement en service ambulatoire de l'insuffisance placentaire par héparinisation

Le traitement de l'insuffisance placentaire par héparine est guidé par le principe que l'insuffisance nutritive résultant de la formation d'agrégations thrombocytaires et de dépôts fibrineux sur les villosités, elle peut être améliorée par l'inhibition de ces facteurs de coagulation. Les examens effectués antérieurement dans le cadre d'une étude de l'efficacité du traitement à l'héparine exigeaient l'infusion continue de solutions d'héparine, donc l'hospitalisation des sujets, ce qui, malgré les bons résultats généralement obtenus, ne permet pas l'application de tels examens à grande échelle et retarde d'une façon générale l'intervention thérapeutique.

A la suite des expériences satisfaisantes que nous avons faites dans la prophylaxie post-opérative de thromboses par l'héparinisation à faible dose, nous avons essayé d'appliquer le même traitement pour l'insuffisance placentaire sans hospitalisation prolongée. Pour cela, **nous avons hospitalisé les parturientes soup?onnées d'insuffisance placentaire et leur avons donné des injections sous-cutanées de 5000 IE d.héparine 2–3 fois par jour** selon leur poids respectif. Après leur avoir montré à elles ou à leur mari la technique de l'injection, nous avons continué le traitement en service ambulatoire.

Pour le diagnostic de l'insuffisance placentaire et les contrôles du traitement, nous avons utilisé la céphalométrie ultrasonique, l'estimation d'oestriolurie dans les urines de 24 h. et de HPL (Human Placental Lactogen) et d'oestriol dans le sérum. Nos analyses ont portä sur 13 parturientes'

Le succès de la thérapie s'est manifesté particulièrement par l'augmentation du diamètre bipariétal qui a nettement dépassé le niveau escompté. De même, l'oestriolurie des urines de 24 h. a augmenté parfois plus fortement que dans un déroulement normal de grossesse. Par contre, les analyses d'oestriol et de HPL du sérum ont été moins satisfaisantes. Dans l'ensemble, nos succès thérapeutiques

peuvent être considérés comme relativement encourageants. Dans quelques cas, la thérapie est intervenue trop tard, ou a été de trop courte durée ou est restée sans succès. Un traitement ambulatoire efficace d'héparinisation à faible dose présuppose une thérapie précoce, prophylactique dans les cas douteux et d'une durée suffisamment longue. Dans les cas d'insuffisance placentaire grave, l'hospitalisation et le traitement d'infusion continue à haute dose restent souhaitables.

Pour empêcher un excès d'optimisme, il importe de préciser également que l'inhibition des facteurs de coagulation placentaire ne peut indubitablement constituer qu'une solution partielle du problème de l'insuffisance placentaire.

L'application de cette thérapie nécessite aussi la coopération de la parturiente ainsi que la préparation d'empaquetages d'héparine appropriés et éliminant toute possibilité d'erreur. Conviennent le mieux des petites quantités d'injection au contenu standardisé de 5000 IE d'héparine ou d'ampoules séparées.

D'après nos expériences et les résultats communiqués dans la littérature médicale, il ne semble pas nécessaire d'effectuer des analyses physiologiques de coagulation durant l'application du traitement.

Mots-clés: Héparinisation, insuffisance placentaire.

Bibliography

[1] ANGER, H.: Heparin als Therapiemodell in der Behandlung der Placentainsuffizienz. Fortschr. Med. 92 (1972) 1045

[2] BAERTSCHI, U., J. SCHMID, P. J. KELLER: Der Einfluß von Heparin auf die Placentafunktion. Z. Geburtsh. Perinat. 178 (1974) 111

[3] HALBERSTADT, E.: Persönl. Mitteilung 1974

[4] HOFBAUER, H., W. BUSCH: Die Erfolge einer Dauerheparinisierung bei intrauteriner Mangelentwicklung. In: SALING, E., J. W. DUDENHAUSEN: Perinatale Medizin, Bd. III, Thieme, Stuttgart 1972

[5] LUDWIG, H.: Pathologische Fibrinierung bei Spätgestose. In: RIPPMANN, E. T.: Die Spätgestose, Schwabe, Basel 1970

[6] NICKL, R.: Standardkurven der intrauterinen Entwicklung von Gewicht, Länge und Kopfumfang. Inaugural-Dissertation München, 1972. In: HICKL, E. J., K. RIEGEL: Angewandte Perinatologie, Urban-Schwarzenberg, München 1974

[7] TILSNER, V.: Prophylaxe und Therapie thrombotischer Erkrankungen mit der subcutanen Heparintherapie. Med. Welt 23 (1972) 1553

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