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Radioimmunoassay of SP_1 (Pregnancy-specific β_1-glycoprotein) in maternal blood and in amniotic fluid in normal and pathologic pregnancies*

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During the last years there has been increasing interest in the investigation of biochemical parameters which in addition to placental steroids and peptide hormones might be indicators of placental function and fetal well-being. In this paper we present data on the pregnancy-specific β_1-glycoprotein SP_1 and try to evaluate its clinical significance.

SP_1 was isolated and characterized by BOHN [1, 2]. TATARINOV reported on comparative immunodiffusion investigations which showed identity of his pregnancy specific β-globulin [20, 21] and of PAPP-C of LIN et al. [9] with pregnancy-specific β_1-glycoprotein (SP_1).

SP_1 was characterized as a β_1-glycoprotein with a carbohydrate content of 29% and a molecular weight of 90 000–110 000 [3, 9]. Recently the occurrence of a high molecular weight variant was proposed [25]. The protein is synthesized in the syncytiotrophoblast of the placenta [8, 18] and secreted into the maternal blood in increasing concentrations as pregnancy proceeds [5, 6, 16, 21, 29, 31]. Its detection is possible as early as 18 days after ovulation and hence has been recommended as pregnancy test [6]. The biological function is still unknown. Actually SP_1 is not truly pregnancy-specific. Trace amounts have been detected in nonpregnant individuals [30] and in cultured fibroblasts [13]. Elevated serum levels can arise in patients with trophoblastic and non-trophoblastic malignancies [7, 14, 15, 20, 30].

* Dedicated to Prof. Dr. med. R. KAISER for his 60th birthday

Curriculum vitae

HANNELORE WÜRZ, *Dr. rer. nat., born in Cologne, Germany, graduated from the University of Heidelberg in 1958. After ten years of research in protein- and immunochemistry in several biochemistry departments (Universities of Aachen, Bloomington/Indiana, Yale, Tübingen and Würzburg), she specialized in clinical chemistry. Since 1973 she is working in the Department of Obstetrics and Gynecology, University of Cologne. Current studies: placental proteins, tumour markers, steroidhormone receptors.*

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1 Materials and methods

1.1 Blood samples were taken from healthy pregnant women and from hospitalized and outpatients. Amniotic fluid was obtained from amniocenteses (performed under ultrasonic control) and from deliveries.

1.2 Radioiodination of SP_1

5 µg of SP_1 purified from placenta [4] in 10 µl of phosphate buffered saline were mixed with 0.5 m Ci Iodide in 10 µl of a 125-J-Na-solution (Behringwerke AG, Marburg, FRG; 8–15 Ci 125 J per mg J) and with a suspension of 1 µg Lactoperoxidase (E.C. 1.11.1.7, BOEHRINGER, Mannheim, FRG) in 10 µl PBS. H_2O_2 in 30% solution was used at a 1:10 000 dilution in PBS and 10 µl were added in portions of 1 µl per minute. After a further 10 min. of stirring at room temp. the reaction was stopped by 0.2 ml of 1% NaN_3 in PBS containing 1% bovine serum albumine. The labeled SP_1 was purified by gel filtration on Sephadex G 75 (PHARMACIA, Uppsala, Sweden) and contained approximately 75 µ Ci 125-I per µg SP_1.

1.3 Radioimmunoassay of SP_1

0.1 ml of serum at dilutions of 1:1000 to 1:5000 in PBS plus 1% BSA, 0.2 ml with 0.1 ng of labeled SP_1 and 0.2 ml of monospecific antiserum (from rabbit, charge No. 5756, diluted 1:250.000) were incubated at room temp. for 24–48 hours. Precipitation was achieved by the addition of 0.1 ml of 0.25% rabbit serum and 0.1 ml of 1:16 diluted anti-rabbitserum from donkey (WELCOME Laboratories Beckenham, England), incubation for 18 hours at 4 °C and centrifugation for 30 min at 3000 X g. Serum samples were assayed in duplicates, samples of amniotic fluid (dil. 1:50) in triplicates.

1.4 Radioimmunoassay of HPL

The determination of human placental lactogen in serum was performed with the radioimmunoassay-kit from AMERSHAM BUCHLER (Braunschweig, FRG).

1.5 Determination of SP_1 by radial immunodiffusion

After the 20th gestational week "M-Pargiten-Plates" (OTCE, BEHRINGWERKE) and in early pregnancy especially prepared "Low Capacity Plates" (No. 3551, BEHRINGWERKE) were applied. Lyophylized SP_1 reference sample (OTFL, BEHRINGWERKE) was used as a standard.

2 Results

2.1 Standard curve

The highly sensitive radioimmunoassay, preveously described [30], permits the determination of SP_1 in concentrations from 2 to 200 ng/ml (Fig. 1). The interassay-variation was below 10%. Concerning the specificity, no cross-reaction was observed with HPL, HCG, prolactin or FSH and LH (not depicted in Fig. 1). The immunologic identity of placental SP_1 (standard) and serum SP_1 was indicated by the parallelism of the dose-response curves.

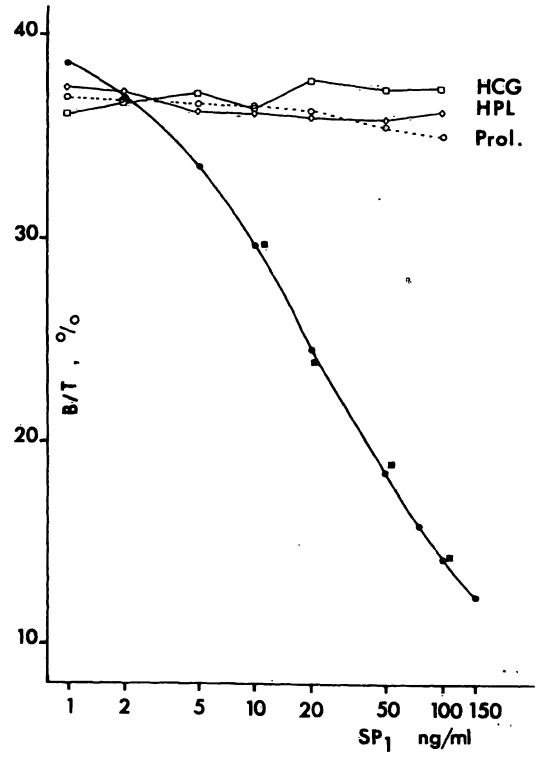

Fig. 1. Standard dose response curve for SP_1. • = Purified SP_1 from placenta, ▪ = Serial dilutions of a late pregnancy serum.

2.2 Normal range

335 single values were assayed from 227 pregnant women from week 3 to 41 of pregnancies which were retrospectively judged to be normal. Fig. 2 shows these single values and a "moving median" (calculated by considering 5 weeks of pregnancy for each time point) and the 10th and 90th percentile. The median concentration rose continuously up to 140 µg/ml in week 36, when a plateau seemed to be formed. A widespread distribution of normal values was then found between 80 and 240 µg/ml. SP_1 concentrations in serial controls of three singleton pregnancies and one twin pregnancy are compared in Fig. 3 by radioimmunoassay and radial immuno-diffusion [11]. With the latter method usually higher concentration values were obtained. The course of the curves was in rather good agreement.

2.3 Complicated early pregnancies

The serum SP_1 concentrations of patients who were admitted to the hospital because of vaginal bleeding are shown in Fig. 4. In this group 73 cases with threatened abortion and continuation of pregnancy, 6 cases of progredient abortion, 5 cases of habitual abortion and 5 cases with subsequent fetal death were evenly distributed within the normal range. Only the group of patients with incomplete abortion exhibited markedly reduced SP_1 levels. 44% of the assay values were below the 10th percentile. The plasma levels from 28 pa-

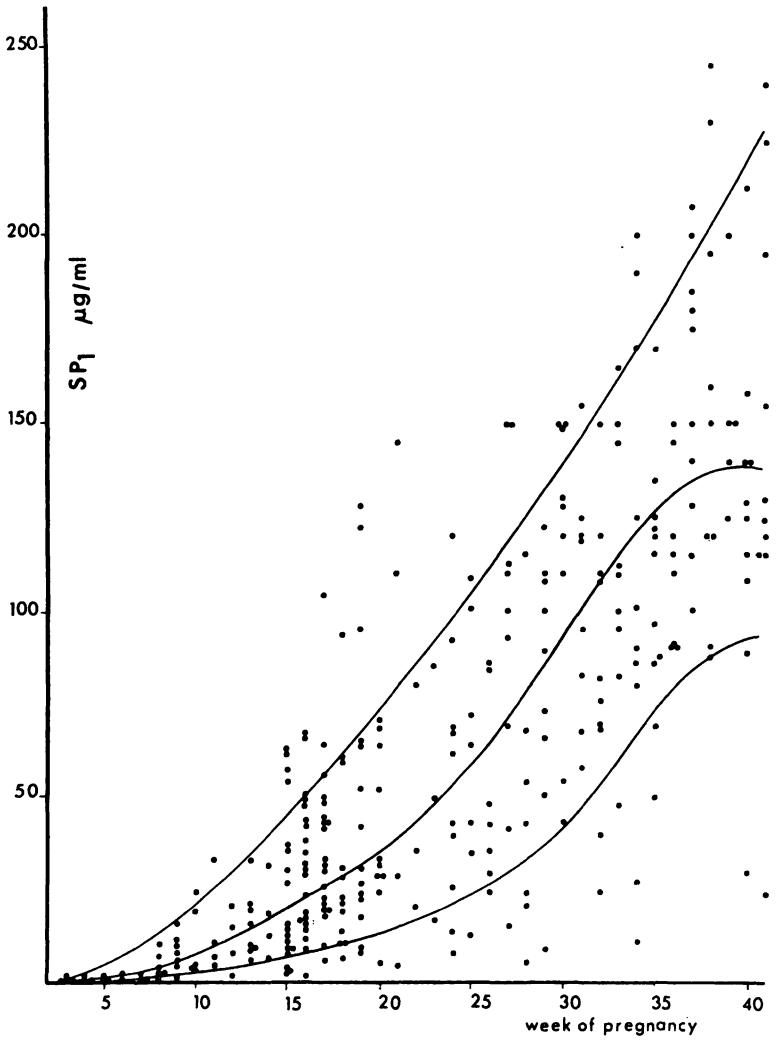

Fig. 2. SP_1 concentrations in maternal plasma in normal pregnancies. (The curves represent the median, the 10th and 90th percentile).

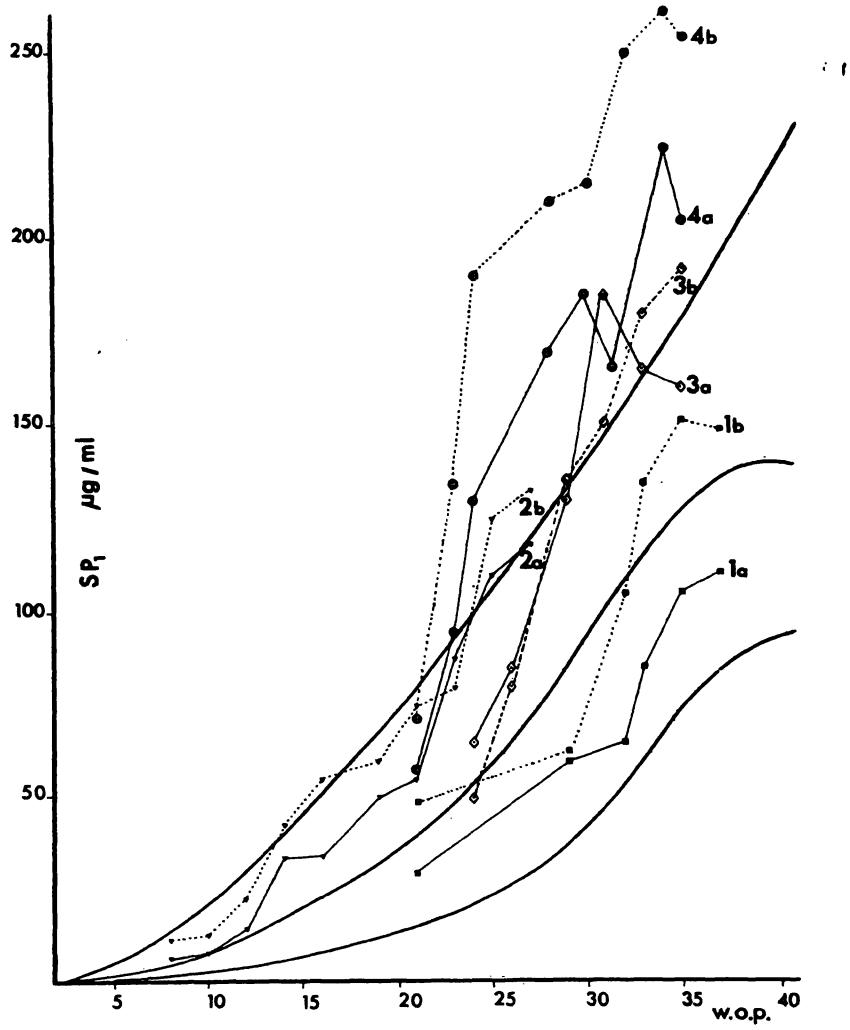

Fig. 3. Serial controls of SP_1 levels in normal pregnancies. (Curves 1,2,3 = singleton pregnancies, curve 4 = twins). The concentration values determined by RIA (a, ——) are compared with radial immunodiffusion (b, - - -).

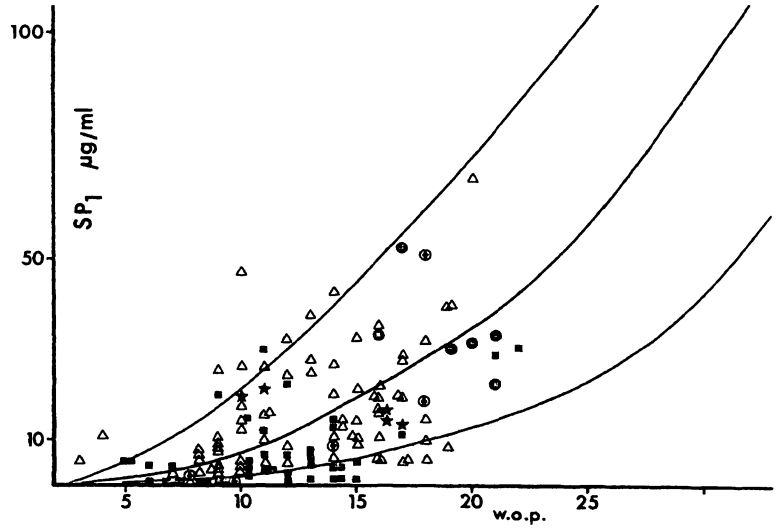

Fig. 4. Serum concentrations of SP_1 in cases of vaginal bleeding in early pregnancy. Single assay values are plotted against the normal range. △ Threatened abortion with continued pregnancy, ● = progredient abortion, ★ = habitual abortion, ■ incomplete abortion, ⊕ = subsequent fetal death.

tients with hyperremesis were analyzed between the 8th and 17th week, 12 assay values were found above the 90% confidence limit, 15 within the normal range and one below the 10% confidence limit.

2.4 Rhesus incompatibility

In serial controls of five patients with Rh-incompatibility the SP_1 values were distributed within the normal range. All the babies were delivered after the 38th week of pregnancy and exhibited only a mild form of erythroblastosis.

2.5 Diabetes

In Fig. 5 the follow-ups of six pregnancies complicated by insulin-dependent diabetes are described. Four of the curves have a similar tendency to steeply increase during the last trimester and all of them showed a marked decline at the time when the termination of the pregnancy was indicated by other clinical parameters. The drop of SP_1 in case No. 6 was associated with fetal death. These changes in concentration concerned only SP_1. HPL and the estrogens remained within their normal ranges. 34 additional samples from 24 individuals were assayed. 17 (50%) were found within the normal range, 3 (9%) above and 14 (41%) below the confidence limits. The trend towards lower values was predominant in the last weeks of pregnancy.

2.6 Stillbirth

In our collective of pathologic pregnancies we encountered seven stillborn children. In all cases the SP_1 level in the maternal blood was below the mean value, in one case below the 10th percentile.

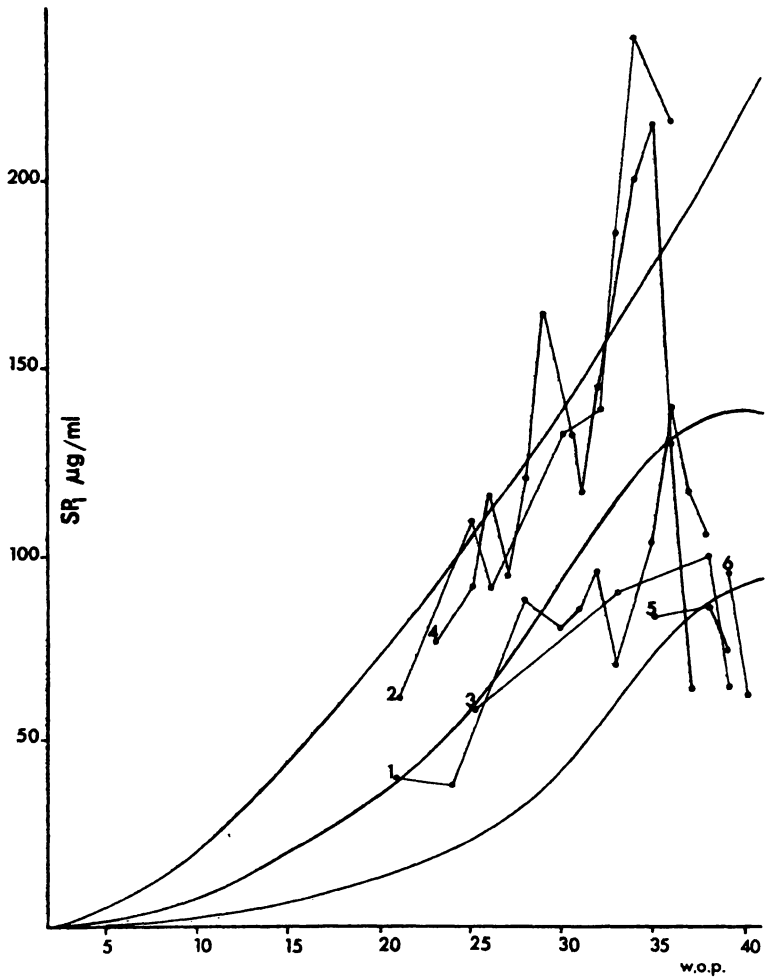

Fig. 5. Serial controls of plasma SP_1 in 6 patients with insulin-dependent diabetes.

2.7 Premature labor

Serial controls of SP_1 and HPL levels were performed in 14 patients being treated with β-mimetic drugs. Before and during treatment the SP_1 values were consitently below the 10th percentile in six cases (two with "small-for-date-babies") and between the 10th percentile and the median in seven patients. The corresponding HPL-values were below the 10th percentile only in the two cases with fetal retardation. The other follow-up curves were evenly distributed within the normal range.

2.8 Fetal growth retardation

A total of 86 plasma samples from 58 individuals was analyzed in risk pregnancies which led to "small-for-date" babies (Fig. 6). Growth retardation was estimated according to the classification of LUBCHENKO et al. [10]. A marked tendency towards reduced SP_1 values was noted: 85% of all cases were found below the median and 45% below the 10th percentile. No differences could be observed between cases with or without the symptoms of dystrophy.

2.9 Gestosis

The data in Fig. 7 were obtained from pregnancies complicated by gestosis in the third trimester. They were devided into A: cases, in which only one or two of the symptoms hypertension, edema and proteinuria were present and B: trisymptomatic forms of EPH-gestosis. Many of these were associated with fetal growth retardation. A considerable scatter with predominantly low SP_1 concentrations was observed.

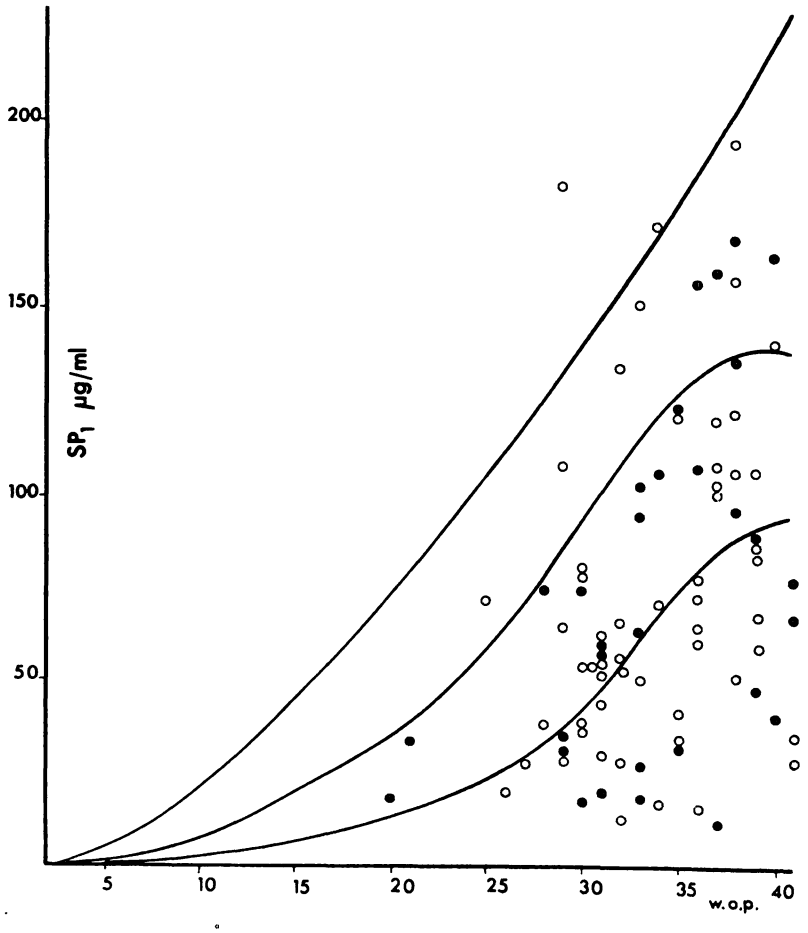

Fig. 6. Concentrations of SP_1 in maternal plasma in pregnancies with "small-for-date" babies (• = with, o = without signs of dystrophy).

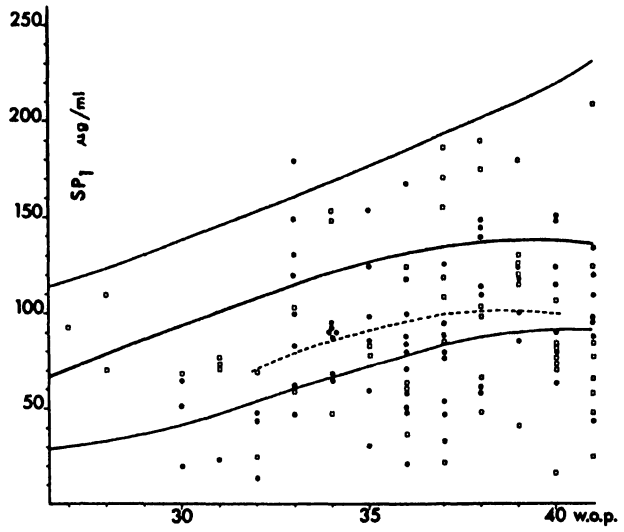

Fig. 7. Serum SP_1 concentrations in cases of EPH-gestosis with one or two (□) and three symptoms (●) as plotted against the normal range. The dotted line represents the median of the assay values in the whole collective of gestosis patients.

	A: 55 cases	B: 71 cases
Below the median:	44 (80%)	60 (85%)
Below the loth percentile:	22 (40%)	27 (38%)

Additionally we compared serial controls of SP_1 and HPL (Fig. 8a and 8b) from 14 patients with EPH-gestosis. Curves 1, 2, 3, 4 and 9 represent the condition of toxemia associated with fetal growth retardation. Case 9 was terminated by fetal death. Many courses of the follow-ups of HPL and SP_1 resemble each other although they are located at different levels of the appropriate normal range. So, curves 2, 6 and 10 give the impression of a normal pregnancy as far as HPL is concerned while the SP_1 concentrations are partially below the 10% confidence limit. In cases 1, 12 and 8 the conditions are vice versa.

2.10 Analysis of amniotic fluid

The distribution of SP_1 concentrations in amniotic fluid during normal pregnancies from week 13 to term is shown in Fig. 9. The mean values and 90% confidence limits are indicated up to the 20th gestational week. Thereafter the small number of samples available allowed only for a rough estimation of the normal range. The SP_1 levels increased from 0.2 µg/ml up to 3 µg/ml and generally represented approximately 1% of the serum concentrations. In Fig. 10 amniotic fluid samples of abnormal conditions are compared with the normal status. From 16 women with RH-incompatibility four exhibited values above and two below the normal range. One serial control curve 1 started with strikingly high values in the 24th week and fell into the upper normal range after week 35. Since the newborn was RH-negative (Anti-D titer 1:32) the incompatibility was of no clinical significance. Curve 2 which is situated within the normal range stems from a patient who developed an

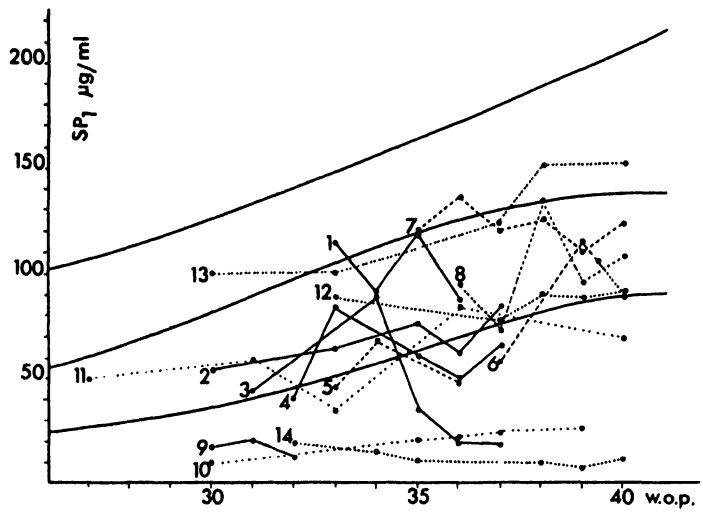

Fig. 8a

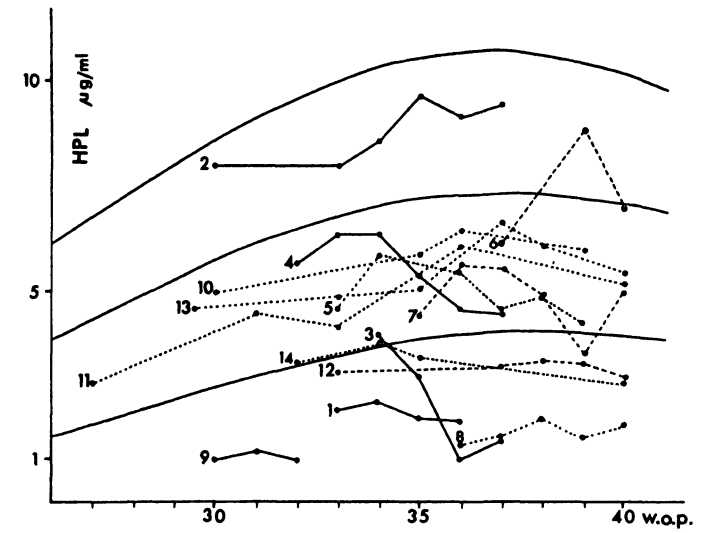

Fig. 8b

Fig. 8. Serial controls of serum SP_1 (a) and HPL (b) from 14 patients with EPH-gestosis. Assay values are plotted against the normal ranges of SP_1 and HPL. Curves 1, 2, 3, 4 represent cases of gestosis associated with fetal growth retardation. Curve 9 = fetal death).

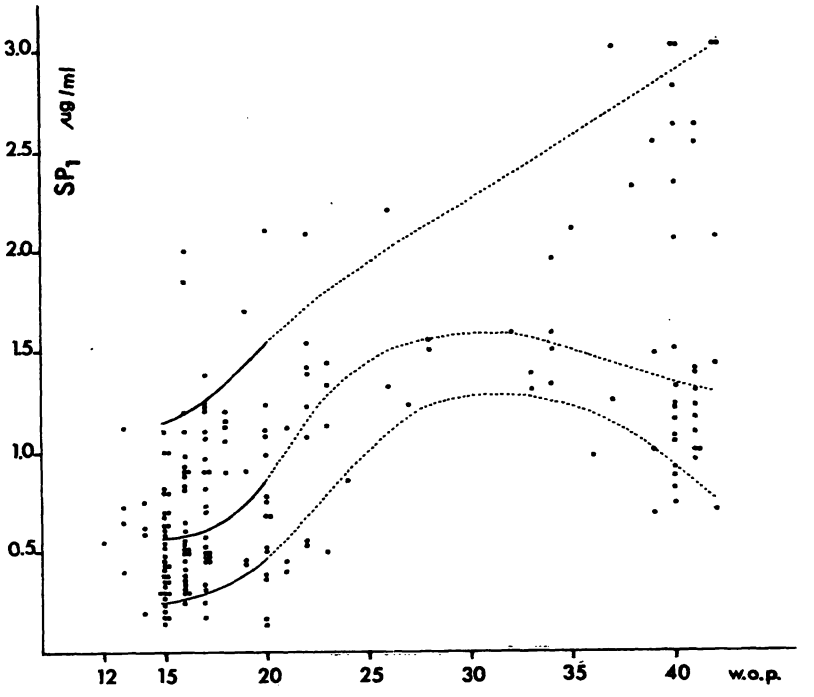

Fig. 9. SP_1 in amniotic fluid in normal pregnancies.

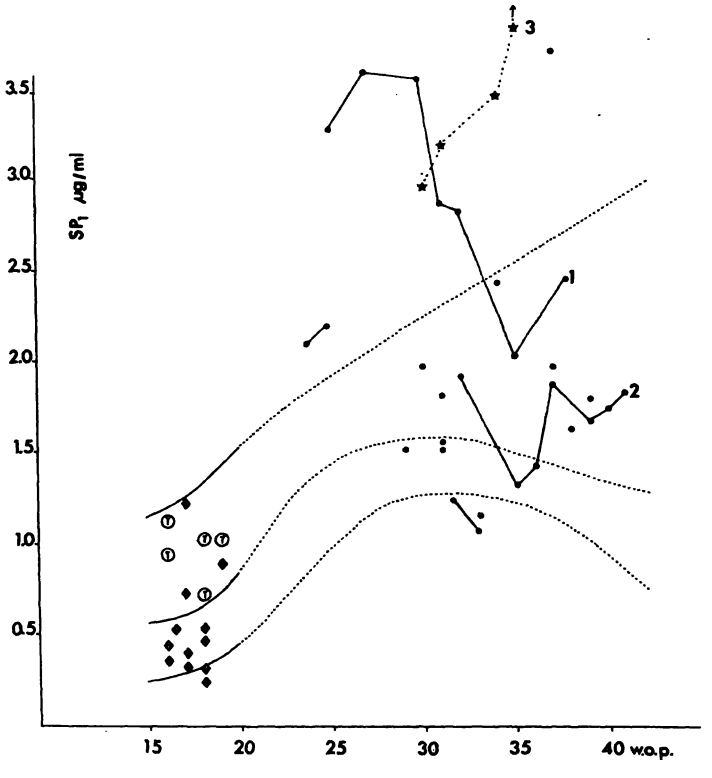

Fig. 10. SP_1 in amniotic fluid in abnormal pregnancies. ● = Rhesus incompatibility, ○ = twins, ♦ = trisomy 21, ★ = congenital mesoblastic nephroma.

anti-D titer of 1:512 and was delivered from a RH-positive child with erhythroblastosis. Curve 3 represents the SP_1 values of a case with the rare diagnosis of a congenital mesoblastic nephroma which was terminated by fetal death. Fetal mongolism was (in 9 from 12 cases) associated with SP_1 concentrations below the mean value. So were two cases of trisomy 18 and one of trisomy 13 (not depicted in Fig. 10). In five twin-pregnancies SP_1 was in the upper normal range. Seven gonosomal anomalies were in the normal range, one was below the loth percentile. Two cases of hydramnios showed elevated levels. From five cases of anencephaly two were above, one below and two within the normal range.

3 Discussion

With the radioimmunoassay described the SP_1 distribution curve of a normal collective of pregnant women was established. The median line increased from 3 µg/ml in the 8th gestational week to 140 µg/ml in the 38th week. Several surprisingly low

levels have been found in the serum of healthy mothers with newborns of normal birthweight. Occasionally very low values were reported by other authors [24, 26] who explained them by the presence of a high molecular weight variant of SP_1, which is not detected by the radioimmunological method which we used.

For the first time the distribution of SP_1 in amniotic fluid was determined throughout normal pregnancies. Concentrations of about 1% of the respective serum value were in agreement with single assay values in this magnitude reported previously [22, 28]. Because of the limited number of samples so far analyzed the limits of the normal range in amniotic fluid could not be determined with accuracy. Out of all the abnormal pregnancies investigated only the cases with trisomies 21, 18 and 13 showed a tendency towards low concentrations. The possible explanation could be a placental distrophy which is frequently associated with fetal mongolism. All twin pregnancies were found above the median, which might be explained by the enlarged placental mass. SP_1 concentrations in gonosomal anomalies and anencephaly are not of predictive value. The SP_1 concentrations in cases of RH-incompatibility were scattered around and within the normal range and cannot assist in the assessment of this disorder. The same holds for the plasma levels in RH-sensitized mothers.

In maternal serum the normal distribution was compared with a variety of pregnancy complications which more or less modified the SP_1 levels. In early pregnancy the SP_1 concentrations were reduced in cases of abortions. In this paper we report only on single assay values. Although these already indicate the pathologic condition, serial controls should be carried out routinely. SCHULTZ-LARSEN et al. [17] have demonstrated the high predictive value of SP_1 for the outcome of pregnancy in cases of threatened abortion. We found, however, cases of progredient abortion also within the normal range. In patients with premature labour low SP_1 concentrations were detected in contrast to normal HPL values, a fact which as yet cannot be interpreted. SP_1 apparently correlates with fetal size. Intrauterine growth retardation led to reduced concentrations in most pregnancies with small-for-date babies. No differentiation, however, was possible between children with or without signs of malnutrition and thus the SP_1 values seem to reflect the placental function better than the condition of the newborn. In follow-ups of patients with EPH-gestosis a marked tendency towards low SP_1 levels was observed. A comparison with human placental lactogen revealed the equal qualities of these two parameters or even the superiority of SP_1 in several cases. These findings are consistent with analogous studies of other investigators [12, 23, 27] and suggest the clinical usefulnes of SP_1 determinations as an additional indicator in the monitoring of high risk pregnancies.

Summary

SP_1, the pregnancy-specific β_1-glycoprotein, was studied in normal and pathologic pregnancies. We developed a highly specific and sensitive double-antibody-radioimmunoassay by radioiodination of purified placental SP_1. This RIA allowed the estimation of SP_1 concentrations as low as 2 ng/mL In a collective of 227 women with normal pregnancies we established the normal distribution curve in maternal plasma from the fifth week of gestation to term. The median value rose steadily from 3 µg/ml in the 8th week to 140 µg/ml in the 36th week when a plateau was formed.

In more than 400 patients with pregnancies complicated by a variety of pathologic disorders the SP_1 levels were controlled by either single assays or serial estimations throughout pregnancy and were compared with the normal distribution range. SP_1 was also determined in about 200 samples of amniotic fluid gained by amniocentesis and during parturition of normal pregnant women from the 13th gestational week until term. The normal range was established up to the 20th w.o.p. The concentrations rose from below 0.2 µg/ml in early pregnancy to 3 µg/ml and generally amounted to approximately 1% of the respective serum value. Pathologic cases with diverse chromosomal anomalies, Rh-incompatibility, anencephaly, hydramnios and other abnormal conditions were examined. From these only twin-pregnancies with slightly elevated levels and cases with fetal trisomies with reduced SP_1 concentrations showed aberrations from the normal distribution. The estimation of serum concentrations in mothers with diabetes or Rh-incompatibility were

not significantly different from the normal collective. **In diabetes a characteristic course of the follow-up curves was observed.**
Abortion in early pregnancy was frequently but not always indicated by reduced SP_1 values. Threatened abortion with subsequent continuation of pregnancy exhibited SP_1 values scattered within the normal range. Since the radioimmunological determination of SP_1 is possible in the early stage of gestation (from week 8) **it may serve as a useful tool for prediction at times when the determination of placental lactogen is not yet possible.** In pregnancies with "small-for-date babies" the correlation between SP_1 in maternal plasma and fetal growth retardation was reflected in a pronounced tendency to low SP_1 levels. Serial determinations of SP_1 in the serum of women with EPH-gestosis were compared with the corresponding HPL determinations and showed the equality of SP_1 concerning the assessment of the placental function.

Keywords: Abortion, amniotic fluid, chromosomal anomalies, pathologic pregnancies, placental function, pregnancy specific β_1-glycoprotein, radioimmunoassay, small for date babies, SP_1, twin pregnancies.

Zusammenfassung

Radioimmunoassay für SP_1 (Schwangerschaftsspezifisches β_1-Glykoprotein) im mütterlichen Blut und im Fruchtwasser während normaler und pathologischer Schwangerschaften
SP_1, das schwangerschaftsspezifische β_1-Glykoprotein, wurde in normalen und pathologischen Schwangerschaften mit einem hochspezifischen und sensitiven Doppelantikörper-Radioimmunoassay untersucht. Die Empfindlichkeit der Methode liegt bei 2 ng/ml. Aus einem Kollektiv von 227 normalen Schwangerschaften mit 335 Einzelwerten konnte eine Normkurve mit Standardabweichungen von der 5. bis zur 40. SSW errechnet werden. Der Medianwert zeigt einen kontinuierlichen Anstieg von 3 µg/ml in der 8. Woche bis 140 µg/ml in der 36. Woche, wonach die Kurve in Form eines Plateaus bis zum Schwangerschaftsende verläuft. Aus 200 Einzelproben von Fruchtwasser, welches durch Amniozentese ab der 13. Woche oder im Laufe der Geburt nach Blasensprengung gewonnen wurde, konnte auch für die SP_1-Konzentration im Fruchtwasser ein Normbereich von der 13. bis zur 20. Schwangerschaftswoche erstellt und für den weiteren Verlauf geschätzt werden. Es zeigte sich ein Anstieg von 0.2 µg/ml bis 3 µg/ml, was einer relativen Konzentration von 1% der korrespondierenden Serumwerte entspricht. An pathologischen Schwangerschaftsverläufen wurden diverse Chromosomenanomalien, RH-Inkompatibilität, Anenzephalie, Hydramnion und andere untersucht. Auffallende Abweichungen von der Norm wiesen nur Zwillingsschwangerschaften mit leicht erhöhten Werten und Trisomien mit eindeutig erniedrigten SP_1-Konzentrationen auf.
Im Serum wurden Einzelwerte oder Verlaufsbeobachtungen der SP_1-Konzentrationswerte bei über 400 Patientinnen mit unterschiedlichen pathologischen Schwangerschaftsverläufen mit dem Normkollektiv verglichen. Die SP_1-Serumkonzentrationen von Müttern mit Diabetes oder RH-Inkompatibilität unterscheiden sich vom Normkollektiv nicht. **Auffällig ist allerdings ein präpartualer Abfall der Verlaufskurven bei Diabetes-Patientinnen.** Bei Blutungen in der Frühschwangerschaft (Abortus imminens) streuen die Fälle mit Fortbestand der Schwangerschaft innerhalb des Normbereiches, während bei späterem Abort die Einzelwerte meist stark erniedrigt sind. **SP_1 scheint ein geeigneter Parameter für die Prognose der Frühschwangerschaft zu sein** und ist hier dem HPL wegen seiner früheren Nachweisbarkeit überlegen. In Schwangerschaften mit "small-for-date-babies" zeigt sich eine Korrelation zwischen der SP_1-Konzentration im mütterlichen Serum und der fetalen Retardierung. Serienbestimmungen von SP_1 im Serum von Frauen mit schwerer Gestose wurden mit den korrepondierenden HPL-Werten verglichen und ergaben die Gleichwertigkeit des SP_1 als Parameter der Plazentafunktion.

Schlüsselwörter: Abort, Chromosomenanomalien, Fruchtwasser, kindliche Wachstumsretardierung, pathologische Schwangerschaftsverläufe, Plazentafunktion, Radioimmunoassay, Schwangerschaftsspezifisches β_1-Glycoprotein (SP_1), Zwillingsschwangerschaften.

Résumé

Dosage radioimmunologique de SP_1 (protéine β_1 spécifique de grossesse) dans le sang maternel et dans le liquide amniotique dans les grossesses normales et pathologiques
A l'aide d'un anticorps double hautement spécifique et sensible nous avons dosé radioimmunologiquement la SP_1, la protéine μ_1 spécifique de grossesse, au cours de grossesses normales et pathologiques. La précision de la méthode est de 2 ng/ml. A partir d'un collectif de 227 grossesses normales avec 335 valeurs individuelles nous avons tracé une courve de normalité avec les déviations standart de la 5ème à la 40ème semaines de grossesse. La valeur moyenne montre une augmentation continue de 3 µg/ml à la 8ème semaine à 140 µg/ml dans la 36ème semaine après quoi la courbe stagne sur un plateau jus-

qu'en fin de grossesse. A partir de 200 plélèvements de liquide amniotique que nous avons obtenus à partir de la 13ème semaine par amniocentèse ou bien pendant l'accouchement après l'amniotomie, nous avons pu obtenir la courbe de la concentration normale de SP_1 dans le liquide amniotique entre la 13ème et la 20ème semaines et faire une estimation quant à son évolution ultérieure. Nous avons observé une augmentation de 0,2 µg/ml jusqu'à 3 µg/ml ce qui correspond approximativement à 1% des valeurs sériques correspondantes. Au cours de grossesses pathologiques nous avons examiné diverses anomalies chromosomiques, des incompatibilités Rhésus, l'anacéphalie, l'hydramnios etc. Les déviations notables de la norme sont observées seulement dans les grossesses géméllaires, avec des valeurs légèrement augmentées et les trisomie, avec des concentrations de SP_1 franchement basses.

Des valeurs individuelles sériques ou bien des observations évolutives des valeurs de SP_1 sur plus de 400 grossesses avec des devenirs pathologiques variés ont été comparées avec les valeurs normales. Il n'y a pas de différences pour les valeurs de SP_1 chez les mères diabétiques et les incompatibilés Rhésus. **Nous avons cepandant observé une chute prépartale des courbes chez les diabétiques.** En cas de saignements en début de grossesse (menace d'avortement spontané) les valeurs des grossessses qui continuent sont dispersées dans la zone de normalité, alors que lorsque la grossesse doit avorter plus tard, les valeurs individuelles sont généralement fortement diminuées. **La SP_1 semble être un paramètre approprié pour le pronostic de la grossesse débutante** est s'avère ici être supérieur à la HPL du fait de sa détection plus précoce. Au cours des grossesse aboutissant à des hypotrophes il existe une corrélation entre la concentration sérique maternelle de SP_1 et le degré d'hypotrophie. Nous avons réalisé des déterminations en série de SP_1 dans le sérum de femme avec une toxémie sévère et les avons comparées aux valeurs de HPL correspondantes; elles ont montré le caractère identique des deux méthodes quant à l'appréciation de la function placentaire.

Mots-clés: Dosage radioimmunologique, évolution pathologique de la grossesse, fausse-couche, anomalies chromosomiques, fonction placentaire, grossesses géméllaires, liquide amniotique, protéine β_1 spécifique de grossesse (SP_1), retard de croissance intrautérin.

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