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MATERNAL PLASMA TOTAL OESTRIOL AND DEHYDROEPIANDROSTERONE SULFATE LOADING TEST AS INDICATORS OF FETO-PLACENTAL FUNCTION OR PLACENTAL SULFATASE DEFICIENCY

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SUMMARY

Serum total oestriol (E_3P) concentrations were measured by radioimmunoassay with I^{125} oestriol after enzymatic hydrolysis, and the range of values were first established in 88 normal singleton pregnancies. E_3P and urinary oestrogen excretion were estimated in 141 high-risk subjects throughout the last trimester of pregnancy and free oestriol determinations were also made in some cases of diabetes on intra-uterine growth retardation (IUGR).

The intra-uterine fetal deaths were easily predictable from E_3P, even in seven cases of toxemia and one of diabetes. The lack of increase of E_3P during the 4 weeks preceding delivery indicates severe fetal hypotrophy and/or malformation.

Total- and free-E_3P and urinary oestrogen excretion were studied in 222 pregnancies with IUGR and their predictive efficacity were compared. The half-life of dehydroepiandrosterone sulfate (DHA-S) and the increase of unconjugated oestradiol (E_2) after IV of the former have been determined in both pregnancies, normal and with retarded fetal development.

The E_2 increases and chiefly the lengthening of DHA-S half-life provide accurate assessment of the utero-placental function and fetal well-being, and obviously allow the diagnosis of placental sulfatase deficiency.

The conclusion of this study is that the assessment of high-risk pregnancies, until now accomplished principally by urinary oestriol assays, may be performed by more convenient and rapid radioimmunoassays of plasma oestriol, and completed in some cases (IUGR, placental sulfatase deficiency) by dynamic tests, chiefly by DHA-S half-life determinations.

INTRODUCTION

The clinical value of measurement of oestrogens to monitor feto-placental function is well established. Advances in radioimmunoassay technique facilitate routine determinations of unconjugated or total oestriol (E_3). However, differences in methods for measurement of E_3, extent of diurnal and random fluctuations in plasma E_3 concentration, and limited appraisal of fetal outcome have obscured the value of this method as an aid in the management of complicated pregnancy. Different authors express different opinions according to whether they attempted to "evaluate the correlation of the assay results with the clinical outcome" or to "ascertain if perinatal deaths and morbidity could be reduced through the knowledge of the oestrogens in maternal plasma" [1].

The present study was undertaken firstly, to know if we could use with a sufficient security the radioimmunoassay of plasma total oestriol concentration (E_3T) for the assessment of the fetal well-being in high-risk pregnancies; and secondly, to compare the predictive efficiency of E_3T and urinary oestrogen (E-ur) in cases of intra-uterine growth retardation (IUGR) and the clinical value of the DHA-S loading test.

I. MATERNAL PLASMA TOTAL OESTRIOL IN NORMAL AND PATHOLOGICAL PREGNANCIES

Since 1965 we have measured total oestrogens in urine (E-ur) by the fluorimetric Ittrich method, and for the last 4 years the determination of human chorionic somatrophin (hCS) has also been made. The former reflects the function of the feto-placental unit, the latter solely the function of the placenta. Until now it has been debatable whether it is more valuable to determine not only the unconjugated but also the total plasma oestriol which is ten times higher than the former, both of them having similar individual and diurnal variations [2, 3]. We have chosen the oestriol RIA kit IM 82 (Radiochemical Center, Amersham) for the assay of the plasma total oestriol in 4 h, after enzymatic hydrolysis but without extraction and using E_3 I^{125} as a tracer, the counting of which is cheaper and quicker than for ^3H.

Our daily routine work concerns nearly 8000 assays but we shall report here only some characteristic observations and the results which have been subjected to computer analysis.

We have first established E_3T levels for normal pregnancies from 301 longitudinal values obtained in 88 patients, judged to be free of complications, as determined by the course of pregnancy and delivery of a term size singleton, who did well during labour and the neonatal period. The normal values have been expressed as percentile established by a non-parametric method. The general shape of the curves, obtained by sequential determination of E-ur or E_3T are similar. This similarity holds true for the increasing levels observed in high-risk patients where pregnancy was normal, as well as for the sustained falls corresponding to seven intra-utero deaths in severe hypertension or preeclampsia between 24 and 31 weeks. The only case where E_3T was more variable than E-ur concerns patients with a severe preeclampsia with marked proteinuria. The results obtained with E_3T are very similar to those obtained by Tulchinsky *et al.* [4] for unconjugated E_3 in ten patients with a preeclampsia with intra-utero death.

E_3T was also (*a posteriori*) as predictive as E_3-ur in an insulin-dependant diabetic pregnancy. We shall discuss later the cases of intra-uterine growth retardation (IUGR) which have been the subject of a particular study. Our conclusions are in agreement with other publications [5] that for a valid indication of fetal well-being serial determinations are essential, and that serum and urinary oestrogens are of comparable predictive value. Indeed, the oestrogen biosynthesis increases significantly at the end of normal pregnancy, this effect being probably due to an increased secretion of DHA-S by the preterm fetal adrenal.

It is evident that a stationary level of E_3T is pathognomonic of a fetal abnormality. It could be due to a severe hypotrophy or associated with a malformation [6], often observed in small-for-gestation-age infant (SGA) (9% in a group of 92 SGA infants recently born in the Maternity of Port-Royal against 2% in the control group). A high rate of major fetal malformations (9.8%) has also been observed by Drew *et al.*[7] in cases of subnormal urinary oestriol excretion. It is therefore necessary to look for those malformations by ultrasonics, and by the assay of α-fetoprotein and bilirubin in amniotic fluid as well as to determine fetal lung maturity before taking a decision about the way of delivery.

We cannot forget in the case of very low levels of E_3T or E-ur the possible occurrence of a sulfatase deficiency, the frequency of which is actually unknown.

We have observed 16 such cases in our laboratory [8]. In most of the cases, *in vivo* loading tests with DHA-S allowed us to make a prenatal diagnosis, which has been confirmed by *in vitro* experiments showing zero, or virtually zero, placental sulfatase activity towards Δ_5P or DHA sulfate. All but two pregnancies were associated with the delivery of male neonates in good health, suggesting that placental sulfatase deficiency is under control of a X-linked recessive character. We cannot conclude from our observations that the defect has an obvious influence on the good outcome of labour, for 10 out of the 16 women delivered vaginally near term [9].

We do not dwell here on the drugs which decrease plasma or urinary levels of oestrogen by several mechanisms: antibiotics as ampicillin which disturbed intestinal glycuro-conjugaison [10, 11], corticosteroids which inhibit the adrenal secretion of C_{19} steroids, but we want to mention our personal observation of a significant decrease of unconjugated oestradiol and of E_3T plasma level as well as of E-ur in patients treated by chlormadinone acetate *per os* for threatened premature labour.

This phenomenon seems to be due to a temporary inhibition of the placental sulfatase without any fetal modification by the synthetic steroid agent.

II. STATISTICAL CORRELATIONS BETWEEN E_3T AND E-ur AND THEIR PREDICTIVE EFFICACITY

The correlation between serum and urinary oestrogen are different according to the authors. The discrepancies are probably due to the methodology employed as well as to distinction not often made between the different types of pathology [5,12–16].

Our study has been done on 141 high-risk pregnancies between 31 and 39 weeks of gestation, consisting of either isolated insulin-dependent diabetics, or diabetes associated with arterial hypertension (HTA), HTA more or less severe, and preeclampsia, IUGR, idiopathic or with HTA, and various disorders or pathological antecedents. Fetal distress was observed in 15 cases (11%) with still-birth in 10 of them; 19 SGA infants were born (14%) from those patients, all of them having been previously suspected. 1075 E_3P assays have been done as well as 1080 E-ur, expressed as mg/oestrogen/g creatinine/24 h. Both assays could be correlated 425 times, when the sample collections have been done on the same day; and the results have been grouped into 3-week periods.

It appears from Table 1 that the correlations are highly significant between E_3T and E-ur in insulin-dependant diabetic pregnancies at every term, and at 32 weeks only, in diabete + HTA. Table 2 shows that the correlations are also significant in HTA, HTA + IUGR and IUGR, between 34 and 39 weeks but not in preeclampsia. It has been previously observed [17] in more than 100 toxemia that patients who respond favorably to clinical management, and in whom the growth of the fetus is not retarded, exhibit normal oestriol level, but in the case of superimposed renal diseases plasma oestriol are abnormally high.

We have also investigated in those 141 patients the relationship between the fetal distress on the one

Table 1. Correlation between total plasma oestriol and 24 h urinary oestrogens (expressed as mg/g creatinine)

	No. of patients	Weeks of pregnancy 34–36 No.*	r	P	37–39 No.*	r	P
HTA	33	6	0.85	<0.05	49	0.31	<0.05
Toxemia	8	6	0.49	N.S.			
HTA + IUGR	21	15	0.58	<0.05	22	0.68	<0.001
IUGR	22	28	0.67	<0.001	18	0.52	<0.05

* Paired samples E_3T/E-ur.

hand, and the levels of E_3T and E-ur on the other.

In this high-risk population, 96% of the women have been hospitalized during pregnancy for varying periods of time and, as indicated previously, 11% have presented fetal distress (meconium stained amniotic fluid, abnormal fetal heart, low apgar score), with still-birth in 10 of them; the mean birth-weight was 2912 g and the mean term of delivery was 38.06 weeks. It is apparent from Fig. 1 that the mean values of E_3T as well as of E-ur are consistently lower than in normal pregnancy. When the mean and S.D., calculated for the groups with and without fetal distress, are compared, there is no statistically significant difference in either plasma or urinary oestrogens between the two groups at any stage of gestation. Moreover, the percentage of normal and low (<10th percentile) E_3T values show an identical distribution of the E-ur between normal and low values (<50% of the mean during the period considered) (Table 3).

The only slight difference is that in cases of fetal distress no one E-ur value was higher than the mean, instead of 2–7% in cases of normal pregnancy, and for E_3T 11–18% are higher than the mean value in cases of fetal distress against 15–23% in normal pregnancies.

It appears then that the same information can be derived from E_3T plasma assays as from oestrogen analysis in urine, but that a single determination could not give unequivocal information on the state of the fetus, a better prediction being afforded by sequential determination of oestrogens in either serum or urine. However, radioimmunoassay is more convenient and rapid, the obvious advantage being the elimination of concern over incomplete collection. With oestriol I^{125} as tracer the counting may be done with a reasonably priced manual apparatus if the number of assays is not too great.

The ante-natal identification of women at increased risk of being delivered of a SGA infant is important because IUGR complicates approximately 5% of pregnancies and has been associated with high perinatal mortality and neurologic sequelae, or, at least, behaviour and mental development abnormalities.

The clinical suspicion of fetal growth retardation can be confirmed by various methods including ultrasound and hormone assays in urine or plasma of the pregnant women (oestrogens and hCS chiefly).

Our purpose was to investigate the predictive value of E_3T and E-ur in cases of suspected IUGR. The clinical diagnosis was made in 222 patients where fundal height was less than would be expected for gestational age at two consecutive ante-natal visits. Centile birth-weights were calculated following Lubencho[18], SGA infants having a birth-weight below the

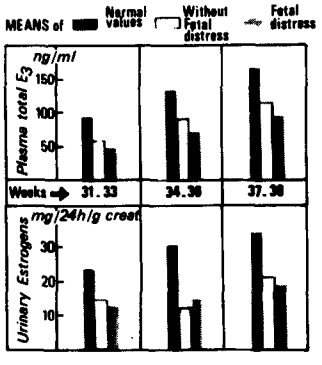

Fig. 1. Plasma total oestriol and urinary oestrogens in normal pregnant women and in high-risk pregnancies with or without fetal distress.

Table 2. Correlation between total plasma oestriol and 24 h urinary oestrogens (expressed as mg/g creatinine) in insulin-dependent diabetic pregnancies

	No. of patients	Weeks of pregnancy 31–33 No.*	r	P	34–36 No.*	r	P	37–39 No.*	r	P
Diabetics	22	35	0.77	<0.001	141	0.73	<0.001	40	0.63	<0.001
Diabetics with hypertension	9	13	0.63	<0.001	18	0.39	N.S.			

* Paired samples E_3T/E-ur.

Table 3. Percentage of normal and low plasma total oestriol and urinary oestrogens in high risk pregnancies with and without fetal distress

	Weeks of pregnancy					
	31–33		34–36		37–39	
Number of patients	Normal (43)	FD (9)	Normal (74)	FD (10)	Normal (88)	FD (7)
E_3TP						
Normal ⩾ 10th percentile	63	56	56	36	63	49
	N.S.		N.S.		N.S.	
Low < 10th percentile	37	44	44	64	37	51
Number of patients	(51)	(9)	(80)	(11)	(82)	(8)
E-ur						
Normal ⩾ 50% of the mean	63	56	51	40	61	57
	N.S.		N.S.		N.S.	
Low < 50% of the mean	37	44	49	60	39	43

tenth percentile (which corresponds approximately to the 3rd percentile in Paris) thus giving a high-risk newborn population.

These 222 patients were delivered of 152 normal birth-weight babies (AGA: adequate-for-gestational age), the mean birth-weight being 2937 g at a mean term of 39.1 weeks, and of 70 SGA infants with a mean birth-weight of 2002 g at 37.8 weeks; namely a clinical predictive value of 32%, which is often obtained when the patients are regularly examined.

The relationship between fetal growth retardation on the one hand, and the levels of E_3T and E-ur on the other hand, is shown in Fig. 2. There appears to be a significant difference between the two populations for both parameters excepted for E_3T at the end of pregnancy.

The percentage of normal and low values are also significantly different between AGA and SGA, except for E-ur at 31–33 weeks and E_3T at 37–39 weeks (Table 4).

It should be noted that if 53–82% of E_3T values are low for SGA as observed by others [17, 19], 28–41% of low values are also observed in cases of AGA, the predictive value of a low E_3T being 41–45% according to the gestational age. The predictive values of E-ur is lower, 37–41%.

We were interested to see if the combination of the two parameters increases the precision of the diagnosis. Indeed, we did not observe any SGA infants with normal E_3T and E-ur, nor with low E_3T and normal E-ur. Fetal growth retardation is the most likely result when both of the tests were low at the same time; but the combination of E_3T and

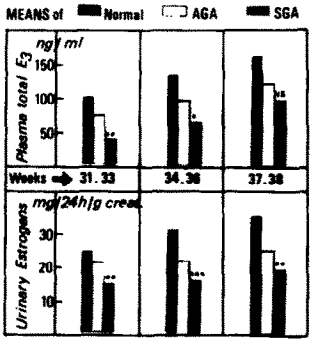

Fig. 2. Plasma total oestriol and urinary oestrogens in normal pregnancy and in suspicion of intra-uterine growth retardation, with (SGA) and without fetal hypotrophy (AGA).

Table 4. Percentage of normal and low plasma total oestriol and urinary oestrogens in suspicion of intra-uterine growth retardation with (SGA) and without (AGA) fetal hypotrophy

	Weeks of pregnancy					
	31–33		34–36		37–39	
Number of patients	AGA (40)	SGA (11)	AGA (58)	SGA (23)	AGA (47)	SGA (17)
Plasma total E_3						
Normal ⩾ 10th percentile	72	18	59	26	72	47
	$P < 0.01$		$P < 0.01$		N.S.	
Low < 10th percentile	28	82	41	74	28	53
Number of patients	(59)	(31)	(85)	(49)	(73)	(38)
Urinary oestrogens						
Normal ⩾ 50% of the mean	76	58	69	41	67	47
	N.S.		$P < 0.01$		$P < 0.05$	
Low < 50% of the mean	24	42	31	53	33	53

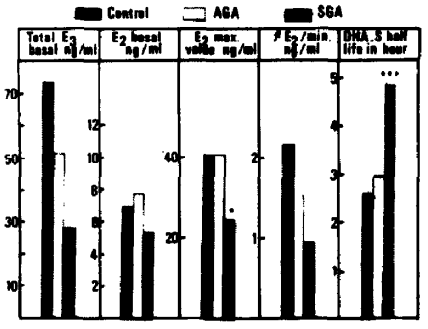

Fig. 3. Mean values of the results obtained before and after dehydroepiandrosterone sulphate (DHA-S) loading test in 29 control pregnancies and in 23 suspicions of intra-uterine fetal growth retardation (16 AGA and 7 SGA infants).

E-ur does not improve the predictive value, demonstrating once again that the same information can be derived from E_3T plasma assays as for the urinary oestrogen analysis.

III. DEHYDROEPIANDROSTERONE SULFATE (DHA-S) LOADING TEST

In a complementary approach we have more recently investigated the diagnostic value of the placental function by intravenous administration of 50 mg DHA-S to the mother.

The oestrogen increase in plasma or urine was taken by Lauritzen as a measure of the placental capacity for oestrogen biosynthesis which was assumed to run parallel to other placental functions of vital importance for fetal well-being [20, 21].

In practice, several modifications of this loading test can be proposed, including the metabolic clearance rate of DHA-S [22] and its metabolic clearance into plasma E_2 [23] (these two determinations needing the use of radioactive tracer), which reflect utero placental perfusion and enzymatic placental activity.

The same type of information can be obtained by the half-life of DHA-S determined by radioimmunoassay [24], which, as such, may provide an assessment of the placental function in a variety of clinical conditions. We have compared the predictive efficacity of the E_2 and E_3T-P basal value, the maximal increase of E_2 and its rate per minute during the first 15 min, after the injection [25], and the DHA-S half-life, for the diagnosis of fetal hypotrophy, the test being done at a mean term of 34 weeks.

The study has been carried out in 29 control pregnancies including 13 threatened premature labours, and 8 strictly normal pregnancies (group I). The 23 suspicions of fetal growth retardation can be separated into two groups corresponding to 16 infants with normal birth weights for gestation age (group IIA), and 7 SGA newborns (group IIB).

Figure 3 and Table 5 show that E_2 is similar in groups I and IIA, smaller in IIB, but without significant difference.

E_3T is maximal in control group, lowest in the case of SGA infants. The difference is not significant, but as seen previously, E_3T values are lower than the mean at this period when a fetal growth retardation

Table 5. Results obtained before and after DHA-S loading test, performed at mean term of 34 weeks in various clinical conditions

Number	Term delivery (weeks)	Birth-weight (g)	Basal level E_2 (ng/ml)	Basal level E_3T (ng/ml)	After DHA-S injection E_2 (max. value, ng/ml)	After DHA-S injection ΔE_2 (ng/ml/min.)	After DHA-S injection E_2/min. (ng/ml)	DHA-S half-life (h)
				I. Control				
29	38.50 ±1.6	3070 ±420	7.10 ±5.17	74.12 ±73.7	41.5 ±17.2	34.0 ±14.2	2.23 ± 2.98	2.87 ± 0.81
				II. Suspicion of intra-uterine growth-retardation				
(A) Normal birth-weight								
16	39.0 ±1.2	2860 ±300	7.92 ±3.35	52.06 ±31.6	41.7 ±18.3	36.3 ±18.1	1.60 ± 1.22	3.06 ± 0.64
(B) Small-for-date infants								
7	36.6 ±2.6	1730 ±510	5.41 ±3.45	28.86 ±16.41	25.3* ±6.5 ($P = 0.02$)	19.9* ±3.6 ($P = 0.025$)	1.01 ± 0.52***	4.94 ± 0.57*** ($P < 0.001$)
				III. Sulfatase deficiency				
Pio	39	2510	2.5	4.0	3.7	1.2	nil	30
Cor	40	3140	2.2	2.0	7.4	5.2	0.013	>15
Ma	40	3400	5.2	5.0	6.6	1.4	0.08	2.73
				IV. Long-term corticotherapy				
Mez	36	2660	3.9	11.0	30.4	19.4	1.39	2.73
Val	33	1000	2.8	33.0	18.0	15.2	0.63	4.29

* $P < 0.01$.
** $0.01 < P < 0.001$.
*** $P < 0.001$.

is clinically suspected, and for SGA all the values are below the 5th percentile established previously in normal pregnancies (52 ng/ml at 34–36 weeks), the predictivity of these low values being 50%.

The mean of the maximum E_2 value observed after DHA-S injection is identical in control group and group IIA, the lowest being in group IIB, with a significative difference of $0.01 < P < 0.05$. In cases of SGA, all E_2 values are lower than 41.5 ng/ml which is the mean value in control group.

Similar results are obtained for ΔE_2 (difference between E_2 max. and its basal level) which is always below 34 ng/ml (mean for control pregnancies) in the 7 cases of SGA. The rate of E_2 increase during the first 15 min after DHA-S injection does not seem to be so predictive; it is the highest in group I and the lowest in group IIB, but without a significant difference. On the other hand, DHA-S half-life is similar in group I and IIA and significantly longer in group IIB ($P < 0.001$). In the 7 cases of SGA the half-life is higher than 4.2 h, values which correspond to the 95th percentile determined for the 45 other pregnancies, and considerably higher than the mean value in control group (2.87 h).

It thus clearly appears that DHA-S half-life is the best criteria of intra-uterine growth retardation (78% of SGA if it is longer than 4.2 h, 0% if it is shorter).

The DHA-S loading test permits in addition the diagnosis of sulfatase deficiency. In such cases, the E_2 increase is very small, almost nil, and the DHA-S half-life mostly very long. In cases of long-term corticotherapy for maternal diseases, where urinary and plasma oestrogens are very low, the DHA-S loading test allows the determination of fetal well-being as shown in Table 5, where you can see the low E_2 increase and the long DHA-S half-life in cases of fetal distress and hypotrophy (Val) contrasting with normal results in normal pregnancy treated by corticoids (Mez).

In conclusion, the measurement of total plasma oestriol (particularly when done on serial samples) and the measurement of the DHA-S half-life, can be of considerable help in the management of high risk pregnancies, particularly in case of intra-uterine growth retardation.

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REFERENCES

1. Duenholter J. H. and MacDonald P. C.: Correspondance. *Am. J. Obstet. Gynec.* **129** (1977) 471–474.
2. Klopper A.: Choice of hormone assay in the assessment of feto-placental function. In *Endocrinology of Pregnancy* (Edited by Fuchs and Klopper). 2nd Edn. Harper & Row (1977) pp. 350–364.
3. Klopper A. J., Wilson G. R. and Masson G. M.: Observations on the variability of plasma estriol. *Obstet. and Gynec.* **49** (1977) 459–461.
4. Tulchinsky D., Karow W. G., Gentry W. C. and Okada D. M.: Plasma steroids in the assessment of normal and abnormal pregnancy. In *Exploration Hormonale de la Grossesse*. Edition Sepe, Paris (1974) pp. 523–543.
5. Giorgi E. P., Gore M. B. R. and Tye G. M.: Comparison of maternal serum and urinary estrogen determinations as indicators of fetal well-being. *Annls Biochem.* **14** (1977) 335–342.
6. Sybulski S., Assward A. and Maughan G. B.: Maternal estrogen levels in two pregnancies complicated by severe fetal growth retardation with congenital anomaly. *Am. J. Obstet. Gynec.* **125** (1976) 864–867.
7. Drew J. H., Abell D. A. and Beischer N. A.: Congenital malformation, abnormal glucose tolerance, and estriol excretion in pregnancy. *Obstet. Gynec.* **51** (1978) 129–132.
8. Bedin M., Alsat E., Tanguy G. and Cedard L.: Deficit en sulfatase placentaire in Perinatal Endocrinology and Parturition. Colloque Inserm, Paris (1978).
9. Bedin M., Alsat E., Tanguy G. and Cedard L.: Placental sulfatase deficiency: Clinical and biochemical study of 16 cases. *Eur. J. Obstet. Gynec. Reprod. Biol.* **77** (1978) 169–180.
10. Willman K. and Pulkkinen M. O.: Reduced maternal plasma and urinary estriol during ampicillin treatment. *Am. J. Obstet. Gynec.* **109** (1971) 893–896.
11. Adlercreutz H., Martin F., Lehtinen T., Tikkanen M. J. and Pulkinen M. O.: Effect of ampicillin administration on plasma conjugated and unconjugated estrogen and progesterone levels in pregnancy. *Am. J. Obstet. Gynec.* **128** (1977) 266–271.
12. Dubin N. H., Crystle C. D., Grannis G. F. and Townsley S. D.: Comparison of maternal serum estriol and urinary estrogen determination as indices of fetal health. *Am. J. Obstet. Gynec.* **115** (1973) 835–841.
13. Aickin D. R., Smith M. A. and Brown J. B.: Comparison between plasma and urinary oestrogen measurements in predicting fetal risk. *Aust. N.Z. J. Obstet. Gynec.* **14** (1974) 59–76.
14. Hähnel R. J.: Comparison of plasma and urinary oestrogens in pregnancy. *Aust. N.Z. J. Obstet. Gynec.* (1974) 12–22.
15. Miller C. A., Fetter M. C., Bogulavski R. C. and Heiser E. W.: Maternal serum unconjugated estriol and urine estriol concentrations in normal and high-risk pregnancy. *Obstet. Gynec.* **49** (1977) 287–291.
16. Ylikorlala O., Haapalahti J. and Jouppila P.: Comparison between serum estriol and urinary estrogens as indice of feto-placental function. *Arch. Cynäk.* **221** (1976) 179–185.
17. Levitz M. and Young B. K.: Estrogens in pregnancy. In *Vitamins and Hormons*. Academic Press, New York (1977) pp. 109–147.
18. Lubchenco L. O., Hansman C., Dressler M. and Boyd E.: Intrauterine growth as estimated from live born birth-weight data at 24 to 42 weeks of gestation. *Pediatrics* **32** (1963) 793–800.
19. Edwards R. P., Diver M. J., Davis J. C. and Hipkin L. J.: Plasma oestriol and human placental lactogen measurements in patients with high risk pregnancies. *Br. J. Obstet. Gynec.* **83** (1976) 229–237.
20. Lauritzen C.: Conversion of DHEA sulfate to estrogens as a test of placental function. *Horm. Met. Res.* (1969) 1–96.
21. Strecker J. R., Killus C. M., Lauritzen C. and Neumann G. K.: The clinical value of the dehydroepiandrosterone sulfate loading test in normal and pathologic pregnancies. *Am. J. Obstet. Gynec.* **131** (1978) 239–249.
22. Gant N. F., Hutchinson H. T., Siiteri P. K. and McDonald P. C.: Study of the metabolic clearance rate

of dehydroisoandrosterone sulfate in pregnancy. *Am. J. Obstet. Gynec.* **111** (1971) 555–569.
23. Madden J. D., Siiteri P. K., McDonald P. C. and Gant N. F.: The pattern and rates of metabolism of maternal plasma dehydroisoandrosterone sulfate in human pregnancy. *Am. J. Obstet. Gynec.* **125** (1976) 915–920.
24. Cohen H. and Cohen M.: DHA-S half-life in pregnancy, its prognostic value in high risk pregnancies. *J. steroid Biochem.* **8** (1977) 381–383.
25. Thoumsin H. J.: Exploration dynamique par le test du DHEA.S de la production oestrogénique au cours du 3ème trimestre de la gestation. Thèse de Doctorat Es Sciences Cliniques (1977) Université de Liège.