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The influence of betamethasone on the feto-placental unit
A preliminary report*

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Curriculum vitae

RADU IOAN NEGULESCU *was born in 1941. 1959–1965 studies in medicine at the University Medical School Cluj-Napoca, Romania. 1964–1967 internship at the University Clinic Cluj-Napoca and since 1969 resident in obstetrics and gynecology. 1974 Dr. med. sci. after studies on EPH-gestosis. 1975–1976 Humboldt-research fellow at the Department of Obstetrics and Gynecology, University of Ulm. Current studies on the influence of corticosteroids on the feto-placental unit.*

The prophylactical treatment of respiratory distress syndrome with betamethasone is used successfully in many clinics [2, 6, 19, 20, 21, 27]. A disadvantage of betamethasone administration is the regular fall of estrogen levels in maternal urine or plasma, which may lead to difficulties in the evaluation of the fetal condition in pregnancies at risk.

SIMMER et al. [24] and OHRLANDER and GENNSER [18] have studied steroidgenesis in the fetoplacental unit following corticosteroid injection. They could show a decrease of total estrogens in 24-hour-urine. OHRLANDER [18] and GENNSER [8] where able to demonstrate a decrease of cortisol in maternal and fetal plasma and amniotic fluid following betamethasone injection. ARAI [1] reported a drop of estrogens in maternal and fetal plasma after intramuscular injection of dexamethasone into the fetus in utero. TOWNSLEY [29] showed a 19% reduction of estrogen excretion in 24-hour-urine following betamethasone injection to the pregnant baboon. TOMBY RAJA [28] injected betamethasone in order to reduce estrogen levels as a treatment to prevent premature labour.

In our investigations we wanted to examine the influence of betamethasone on estrogen-biosynthesis in the placenta and fetus. To our knowledge there is no study examining the changes of steroid hormone levels in maternal plasma in short intervals after betamethasone injection to the mother. **Furthermore we wanted to know wether the changes of estrogen concentration in plasma following betamethasone administration to the mother could be of use as a new dynamic functional test of the placenta and the fetus.** It was also planned to test the steroidbiogenetic-function of the placenta after betamethasone suppression of the fetal pituitary-adrenal axis by DHA-S loading.

1 Material and methods

We used Celestan Solubile made by BYK ESSEX, 1 ml containing 5.3 mg. betamethasone-sodium-

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phosphate, representing 4 mg. betamethasone.

Maternal plasma concentrations of estrone (E_1), estradiol-17-beta (E_2), estriol (E_3), cortisol and total estrogens in 24-hour-urine where determined in normal and pathological third trimester pregnancies.

A total of 32 volunteers was examined and subdivided into VII groups.

Group I: Three patients with normal uncomplicated pregnancies received 12 mg betamethasone intramuscularly on two successive days.

Group II: Two patients suffering from EPH-gestosis and one from placental insufficiency received 12 mg betamethasone intramuscularly on two successive days.

Group III: Four patients with normal pregnancies received 8 mg betamethasone intravenously.

Group IV: Three patients with normal pregnancies received 8 mg. betamethasone and an additional 25 mg DHA-S intravenously three hours later.

Group V: Two patients with pathological pregnancies (placental insufficiency) received 8 mg betamethasone. Three hours later they received 25 mg DHA-S intravenously.

Group VI: Four patients with normal pregnancies received 8 mg betamethasone. 50 mg DHA-S were given intravenously 30 minutes later.

Group VII: Six patients with normal and six with pathological pregnancies (placental insufficiency) received 8 mg betamethasone and an additional 50 mg DHA-S intravenously three hours later.

Collection of 24-hour-urine for determination of total estrogens was performed the day before injection and during the six following days.

Maternal venous blood for determination of E_1, E_2, E_3, as well as cortisol was drawn before injection of betamethasone and at short intervals during the first day of treatment (see figures for exact timing) and one hour after the second injection on day 2 in groups I and II. One blood sample was drawn on each of the six subsequent days at 9 a.m. The plasma was separated by centrifugation at 3000 rpm and stored frozen until used for the assay.

Radioimmunoassays of E_1, E_2 and E_3 were performed with specific antibodies which were a gift from Dr. GOEBEL, München and Dr. KÜNZIG, Köln. The assay procedure was described previously [25]. Different volumes of undiluted plasma were extracted with 10 volumes of ether for determination of the unconjugated estrogen fractions. A photometric method was employed to determine the total urinary estrogens. Unconjugated cortisol was determined by the method of MURPHY [16].

2 Results and discussion

The basal values of E_1, E_2, E_3 in maternal plasma were considerably higher in normal pregnancies compared to pathological pregnancies (Fig. 1, 2).

Following injection of betamethasone, plasma and urinary concentrations of estrogens decrease because of diminished adrenocortical precursor availability in the fetal and maternal compartment [23, 24].

The decrease of plasma-estrogens, cortisol and of the urinary-estrogens is dose-dependent and reaches a maximum after the second betamethasone injection. A greater percentage of the total diminuition in plasma estrogens is observed three hours after the first betamethasone injection (Fig. 1,2,4). The investigation of plasma estrogen changes following betamethasone shows a great difference between normal and pathological pregnancies. **The decrease of E_2 three hours after intramuscular injection of betamethasone was 69% of control values in normal compared to 33% in pathological cases. The drop of E_3 was also more prominent in normal pregnancies (63%) compared to complicated cases (42%),** (Fig. 1, 2).

In normal pregnancies it took 3 days for estrogen values to return to basal levels. In pathological pregnancies 5 days were required before basal values were attained. Thus pathological cases seem to reach preinjection control estrogen values later than normal pregnancies. Plasma E_3 concentrations need the longest time to return to basal values. This could be caused by a longer suppression of the fetal than of the maternal pituitary-adrenal axis [24]. Betamethasone may produce suppression of 16λ-hydroxlase in the fetal liver without influencing the placental aromatisation.

In one case of EPH-gestosis and intrauterine fetal death, concentrations of E_1, E_2, and E_3 showed little change following betamethasone in contrast to normal control cases. A more pronounced

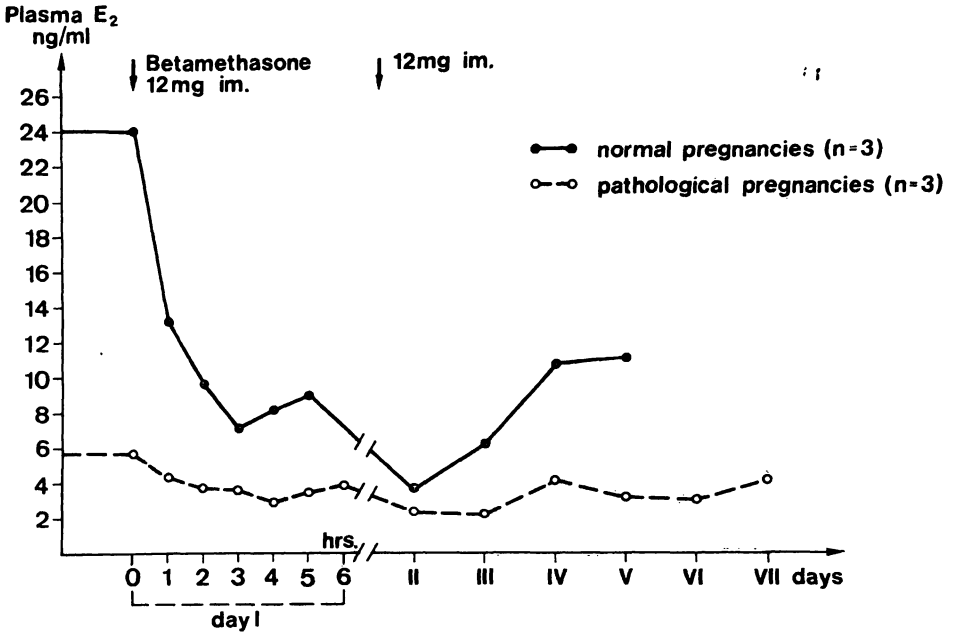

Fig. 1. Plasma estradiol-17-β after betamethasone administration in normal and pathological pregnancies. Mean values. *Normal*: base values = 20–40–12 ng/ml, SD = 14.42; 3 hrs. after = 6.8–11–4, SD = 3.52. *Pathological*: base values = 8–7–2.3, SD = 3.04; 3 hrs after = 5.2–5.4–0.75, SD = 2.62.

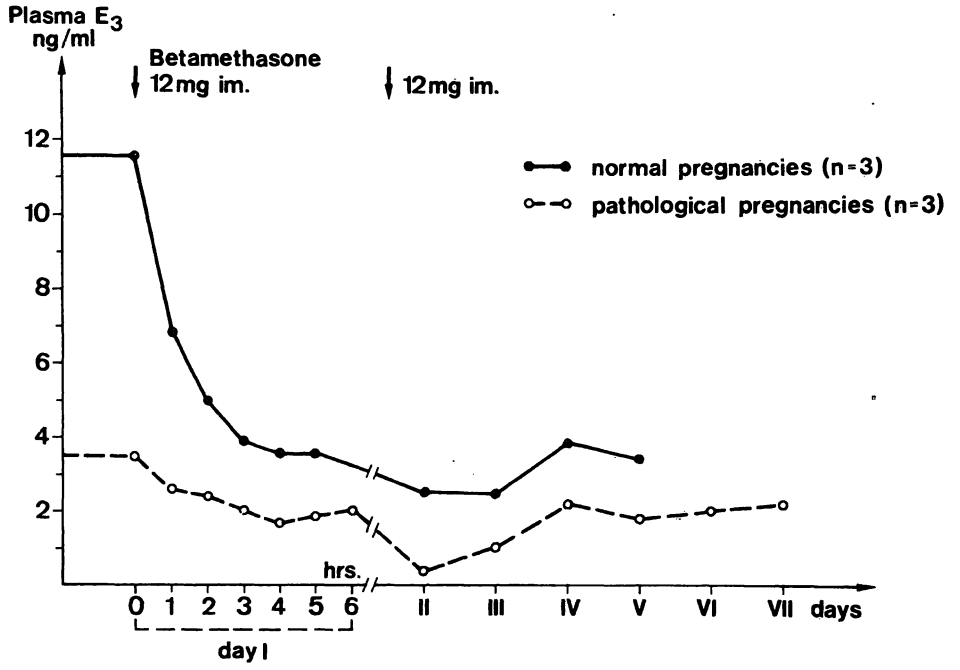

Fig. 2. Plasma estriol after betamethasone administration in normal and pathological pregnancies. Mean values. *Normal:* base values = 12–16–6.8, SD = 4.61; 3 hrs. after = 2.5–7–2.2, SD = 2.68. *Pathological:* base values = 3–5.2–2.3, SD = 1.51; 3 hrs. after = 2.2–3.2–0.70, SD = 1.25.

decrease of plasma estrogens in cases of intrauterine fetal death should be expected if the maternal adrenal cortex is suppressed to a major extent.

In contrast to the studies of ÖHRLANDER [18], who described a return to basal cortisol values after three weeks, we found that a normalisation of cortisol values has already occurred three days

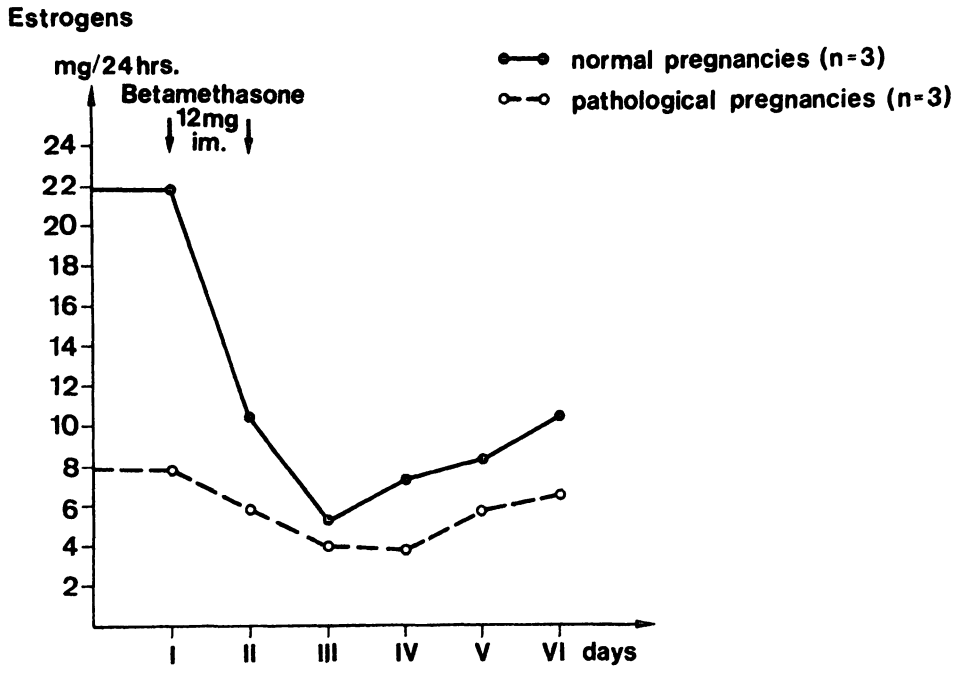

Fig. 3. Total estrogens in 24-h-urine after betamethasone administration. Mean values. *Normal:* base values = 18–27.9–19.7, SD = 5.29; 3 days after = 7.6–3, SD = 3.25. *Pathological:* base values = 5.2–10.6 SD = 3.8; 3 days after = 2–6 mg/24h, SD = 2.82.

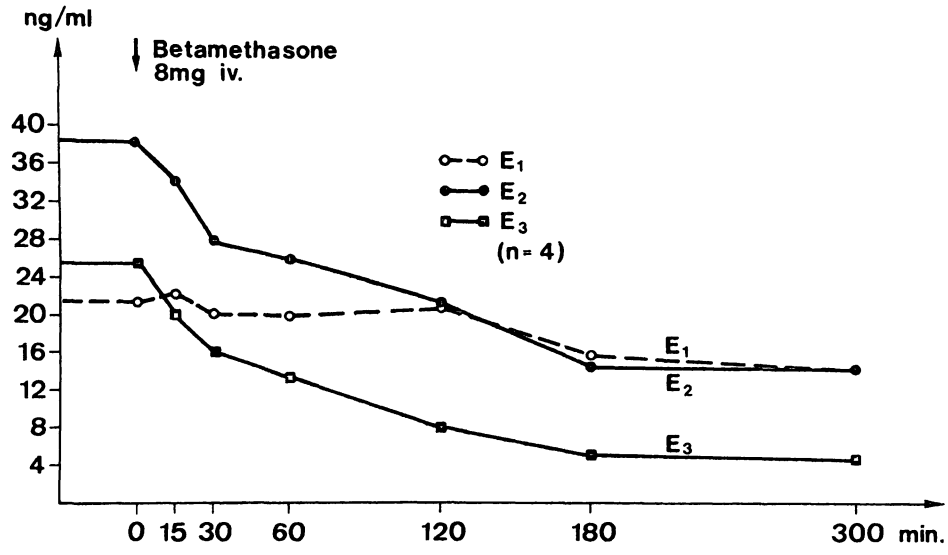

Fig. 4. Estrone, estradiol-17-β and estriol in plasma after iv. injection of 8 mg betamethasone. Mean values of 4 normal pregnancies. *For* E_1 base values = 24–16–30–17, SD = 6.55; 3 hrs. after = 21–16.5–16–10.4, SD = 4.34. *For* E_2 base values = 31–37.5–30–54, SD = 11.09; 3 hrs. after = 20–25–8.5–6.2, SD = 9.03. *For* E_3 base values = 33–17.5–18–34, SD = 9.10; 3 hrs. after = 4.3–1.6–6–7.2, SD = 2.42.

after the second betamethasone application. It is to be stressed however that the cortisol levels in our patients were mostly within normal limits. The concentrations of DHA in maternal plasma and urine show only a small change following betamethasone application in normal and pathological pregnancies [17].

Since the suppression of the maternal adrenal cortex following betamethasone is about the same in normal and pathological pregnancies, one could

draw the conclusion that differences in estrogen decreases are mostly due to the difference in suppression of estrogen precursor-biosynthesis between the normal fetus and the fetus at risk.

Changes of plasma estrogens following betamethasone application correspond well with changes of urinary estrogens (Fig. 3). The maximal mean decrease of urinary estrogens was 76% in normal pregnancies. It was reached the first day after the second betamethasone application. At the same time the maximal drop for the lower control values of pathological pregnancies was only 50% of basal values. The return to basal values was not reached within four days after the second betamethasone injection in both groups.

It has been reported, that the return to basal values is reached in 2–3 weeks [5, 20] or after 5–6 days [21, 22].

Maternal plasma concentrations of estrone (E_1) did not show specific changes during the first days following betamethasone injection.

According to the results from the patients of group IV, V and VI plasma E_2 and E_3 show more pronounced decreases in normal pregnancies than in pathological pregnancies. The E_2 and E_3 increase occurring 30 minutes after DHA-S injection is also higher in normal pregnancies (Fig. 5, 6).

Intravenous injection of 50 mg DHA-S immediately after intravenous betamethasone injection causes a smaller increase of plasma E_3 (since the suppression of the fetal pituitary-adrenal axis is still minimal at this time) than a smaller dose of DHA-S (25 mg) administered three hours later (Fig. 7).

A hypothetical explanation is that endogenous estrogen precursors and exogenous DHA-S compete for aromatisation in the placenta [10, 13, 30].

The increase of plasma E_3 (89%) following DHA-S injection in patients of group IV is quite similar to that in the cases examined by STRECKER and LAURITZEN [25]. BUSTER [3] did not find an increase of plasma E_3 following DHA-S injection. The increase of E_3 after betamethasone inhibition could be explained by an activation of the „phenolic pathway" (16-alfa-hydroxylation in the maternal liver) [7, 22].

The different patterns of plasma concentrations for E_2, E_3 and urinary estrogens following betamethasone and DHA-S injection in normal and pathological pregnancies encouraged us to apply this idea to a new modified dynamic test of feto-placental function: **„A betamethasone suppression-DHA-S stimulation Test"**. We think that this test will give us more and new information about fetal and placental compartments in normal and pathological pregnancies.

The influence of betamethasone on the feto-placental unit is demonstrated in Fig. 8.

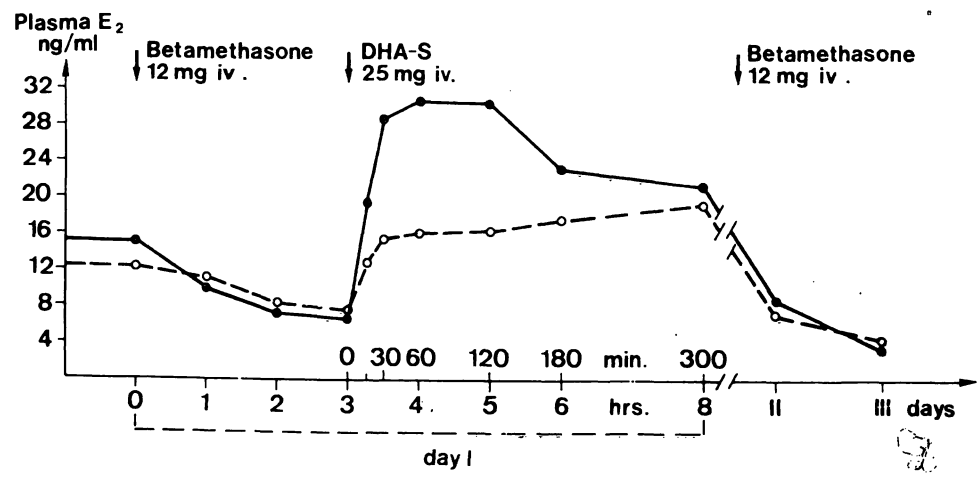

Fig. 5. Plasma estradiol-17-β after betamethasone administration and additional injection of 25 mg DHA-S iv. Mean values. *Normal:* base values = 12–11.6–9.6, SD = 1.28; 3 hrs. after betamethasone = 6.5–2–12.4, SD = 5.2; 30′ after DHA-S = 25–30–30, SD = 2.88. *Pathological* (dotted line): base values = 16 8.5, SD = 5.30; 3 hrs. after betamethasone = 9.5–5.5, SD = 2.82; 30′ after DHA-S = 16–14.5, SD = 1.06.

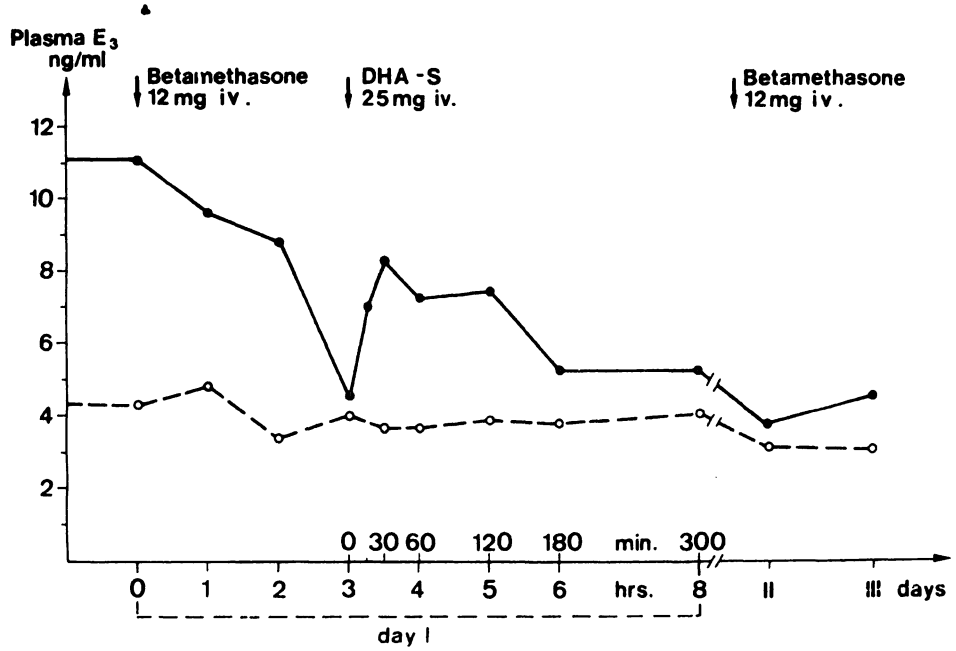

Fig. 6. Plasma estriol after betamethasone administration and additional injection of 25 mg DHA-S i.v. Mean values. *Normal:* base values = 12–11.6–9.6, SD = 1.28; 3 hrs. after betamethasone = 5.8 3.4–4.6, SD = 1.2; 30′ after DHA-S = 10–9–6.4, SD = 1.85. *Pathological* (dotted line): base values = 5–3.6, SD = 0.98; 3 hrs. after betamethasone = 4.1–4, SD = 0.70; 30′ after DHA-S = 3.8–3.6, SD = 0.84.

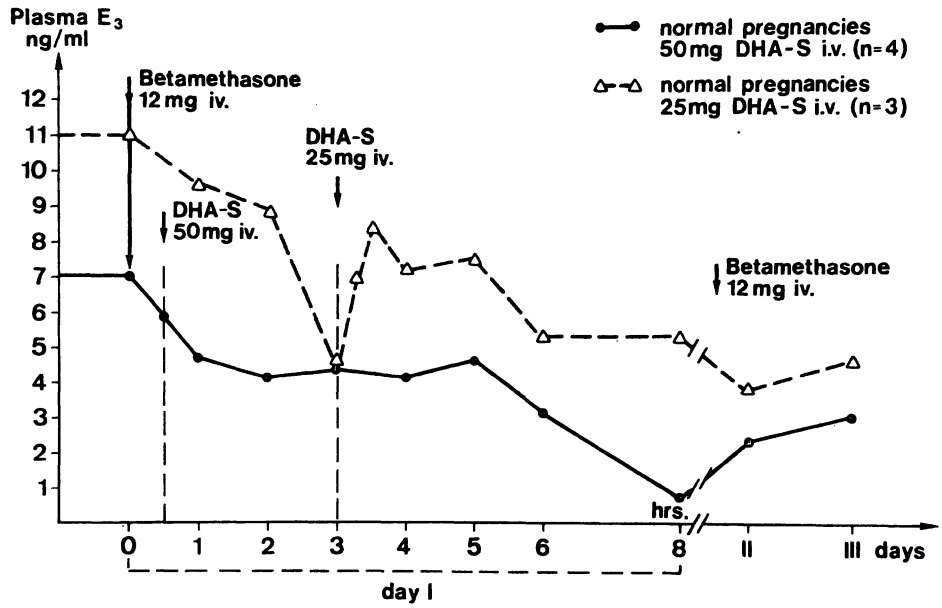

Fig. 7. Plasma estriol after betamethasone administration and subsequent injection of 25 or 50 mg DHA-S in normal pregnancies. Mean values. *For 25 mg* DHA-S the individuel values and SD are identical with values of Fig. 6. *For 50 mg* DHA-S: base values = 8.4–6–6.4–7.3, SD = 1.06; 30′ after betamethasone = 7.6–4.2–4.2–7.6, SD = 1.96; 30′ after DHA-S = 7.5–2.6–5.6–3.2, SD = 2.3.

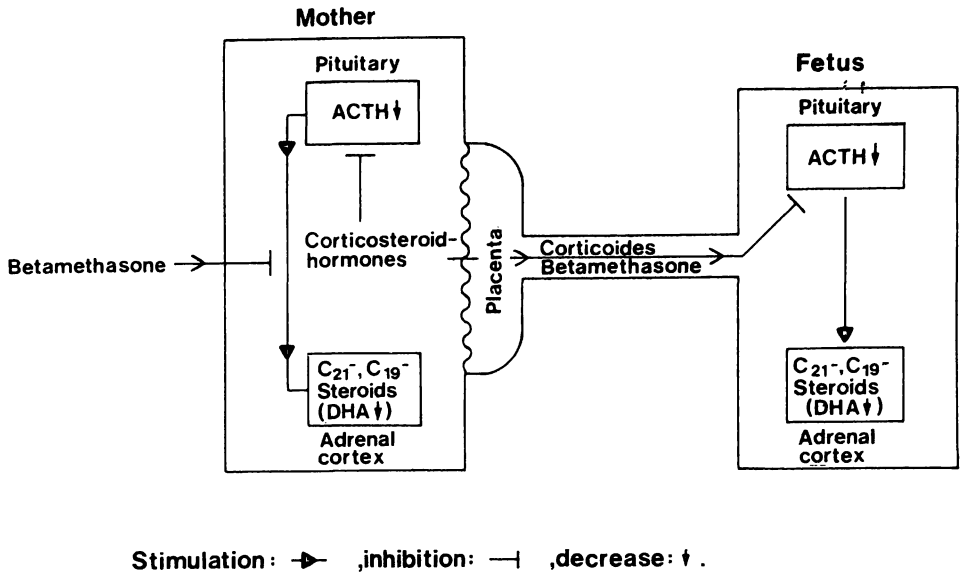

Fig. 8. Schematic outline of the inhibiting effect of betamethasone on steroid production in maternal and fetal adrenals as consequence of ACTH-suppression in the pituitary.

3 Basal theoretical knowledge concerning the test

Investigations of ophorectomized patients have show that there is a minimal basal DHA secretion of the adrenal cortex even after complete suppression of ACTH. Also, it is well known that there is no gonadal DHA production in the fetus. OHRLANDER [18] could show there is minimal estriol excretion in maternal urine (aproximately 2 mg) even after complete suppression of ACTH. These results show the existence of a basal adrenal cortex secretion of estrogen precursors which is independent of hypothalamic-pituitary stimulation. One could say that after suppression of the pituitary-adrenal cortex axis by betamethasone, the determination of plasma estrogens gives information about the basal adrenal secretion of estrogen precursors and the extent of adrenal cortical suppression.

CHALLIS [4] has examined plasma concentrations of androstenedione, testosterone, estrogens and cortisol after betamethasone application to rhesus monkeys. He found a more pronounced suppression of estrogens than androgens. The androgens remained at a constant level after an initial drop. The decrease of estrogens was continual, indicating that it was caused by a suppression of the fetal adrenal cortex.

SIMMER demonstrated [23, 24] that the decrease of C_{19} estrogen precursors following corticosteroid application was more intense in the umbilical vein than in maternal plasma.

We believe that the dynamic determination of maternal plasma estrogens after betamethasone application represents a test for the suppression of the pituitary-adrenal cortex axis.

The following reasons are listed in support of this contention:

1. The extent of the plasma estrogen decrease following betamethasone application shows predominantly the fetal portion of the pool of estrogen-precursors. Maternal precursors show little change.
2. The basal estrogen level that remains constant over a period of time after betamethasone suppression shows preponderately the maternal portion of the pool of estrogen precursors.
3. The extent of the estrogen-fall represents a measure of the fetal pituitary-adrenal suppression and of the ability of the adrenal cortex to respond to factors acting on the feed back mechanisms. This may be important for the adaptation to situations of stress in utero.

4. After maximal suppression of the fetal estrogen precursors, conditions of an "in vivo" isolation of the placenta are created.

In this way it should be possible to evaluate separately e.g. the aromatisation rate of the placenta after DHA-S loading without interference from the fetal or maternal side.

The response of the adrenal cortex to pituitary ACTH depends on the intensity and duration of this stimulation. The adrenal cortex of a normal fetus reacts with an immediate and adequate secretion of corticosteroids. ISHERWOOD and OAKEY [9] could demonstrate an increased production of androgens "in vitro" following ACTH-stimulation. Direct injection of ACTH and HCG into the fetus showed significant rises of maternal estrogens via an increase of fetal estrogen precursors [1, 12, 26].

Animal investigations have shown an increased secretion of ACTH in fetus suffering from chronic or acute hypoxia. There was no rise of plasma-cortisol levels found in fetuses with chronic hypoxia [31].

The estrogen response pattern following betamethasone application changes with the condition of the fetus. A healthy, normal fetus reacts with a more intense decrease of estrogens than a fetus at risk, and the return to values before injection is more rapid.

In normal pregnancies the decline of E_3 three hours after intravenous injection of 8 mg betamethasone exceeds 50% of preinjection values. This decrease showed good correlations to clinical findings, erg. the cardiotocogram and human placental lactogen (HPL).

HPL levels are not influenced by corticosteroid application to the mother [19,20,32]. OHRLANDER [18] could show a direct correlation between basal estriol-excretion in the 24-h-urine and its decrease after betamethasone injection.

In pathological pregnancies the decline of the primarily low estrogen levels is less distinct and the return to basal values is slower.

The most important criteria for the interpretation of the estrogen curves following betamethasone suppression seem to be the extension of the plateau together with the amplitude of the curve and the time required for preinjection control values to be reached.

With an additional application of 50 mg DHA-S three hours after betamethasone injection to the mother and determination of maternal plasma estrogens in short intervals there might be the possibility of a new more sophisticated functional method of determining placental function: "An inhibition test of the fetal pituitary-adrenal cortex axis combined with a loading-test of the placenta."

This test could evaluate the condition of the fetus by determination of E_3 after betamethasone application to the mother and **could also clarify the reserve capacity of the placenta following DHA-S loading,** in a state of maximal suppression of the endogenous estrogen-precursors by determination of E_2 (Fig. 9).

There are numerous reports about the theory and the clinical value of the DHA-S loading-test in plasma [10, 11, 13, 14, 15, 25, 30].

The criteria of normality for this part of the combined test mentioned above agree with those reported by STRECKER and LAURITZEN [25].

In this way an improvement of the DHA-S loading test may be possible since the fetal and to a smaller extent the maternal estrogen precursors are excluded.

The following conclusions can be drawn from our investigations

1. The changes of plasma and urinary estrogen levels depend on the dose of betamethasone and on the way of application.
2. The maximal decrease of maternal E_2 and E_3 is reached three hours after injection. The return to preinjection values takes more than 4–5 days.
3. The decline of estrogens following betamethasone injection to the mother is caused by suppression of adrenocortical estrogen-precursors mainly derived from the fetus.
4. The changes of maternal plasma estrogens after betamethasone and subsequent DHA-S loading offer new possibilities for testing the fetoplacental unit.

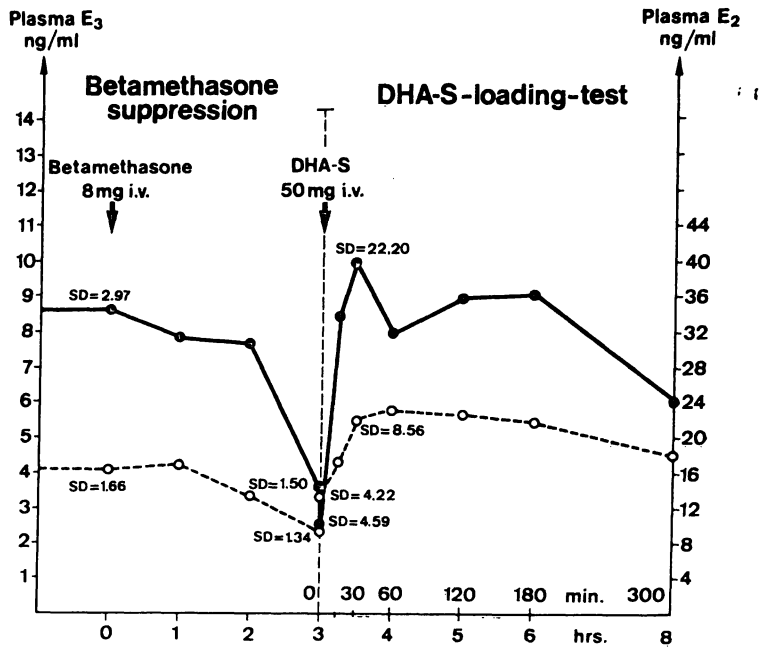

Fig. 9. "A betamethasone suppression DHA-S-loading test". Suppression of plasma estriol after betamethasone administration as index of fetal condition and subsequent evaluation of placental function by DHA-S loading. A hypothesis for a new combined test of fetus and placenta demonstrated in 6 normal and 6 pathological (placental insufficiency) cases. Mean and SD values. For E_3 base and 3 hrs. after betamethasone values $p < 0{,}0025$ (Student test).

Summary

The effect of betamethasone on the estrogen-biosynthesis in placenta and fetus was tested. **It was ashed whether the changes of estrogen concentration in plasma following betamethasone administration to the mother could be of use as a new dynamic functional test of the placenta and the fetus.** It was also planned to test the placental steroidogenetic function after betamethason suppression of the fetal pituitary-adrenal axis, by DHA-S loading.

Maternal **plasma concentrations of estrone (E_1), estradiol 17-β (E_2), estriol (E_3), cortisol and total estrogens in 24-h-urine where determined** in normal and pathological third trimester pregnancies.

A total of 32 patients was examined und subdivided into VII groups. Group I, II and III received 12 mg betamethasone im. or 8 mg iv. Group IV, V, VI, VII received betamethasone and also 25 or 50 mg DHA-S iv.

Maternal venous blood for determination of E_1, E_2 and E_3 as well as cortisol was drawn before injection of betamethasone and at short intervals during the first day of treatment (see figures for exact timing) and one hour after the second injection on day II in the cases of group I and II. One blood sample was drawn on each of the six subsequent days at 9 a.m.

E_1, E_2 and E_3 were determined by radioimmunoassay. A photometric method was employed to determine the total urinary estrogens.

Unconjugated cortisol was determined by the method of MURPHY.

The basal values of E_1, E_2, E_3 in maternal plasma where considerably higher in normal pregnancies than in pathological pregnancies (Fig. 1, 2, 3, 4).

The decrease of plasma-estrogens, cortisol and of the urinary-estrogens is dose dependent and reaches a maximum on the second betamethasone injection (Fig. 1, 2, 3).

Plasma estrogen changes following betamethasone show a great difference between normal and pathological pregnancies. **The decrease of E_2 three hours after intramuscular injection of betamethasone was 69% in normal compared to 33% in pathological cases.**

The drop of E_3 was also more prominent in normal pregnancies (63%) than in complicated cases (42%) (Fig. 1 and 2).

Estrogen values of normal pregnancies returned to basal values three days after injection. In pathological pregnancies 5 days elapsed before values were normal again.

In patients of group IV, V and VI **the increases of plasma E_2 and E_3 occurring 30 minutes after DHA-S injection are also higher in normal that in pathological pregnancies** (Fig. 5, 6).

The different patterns of plasma concentrations of E_2, E_3 and urinary estrogens following betamethasone and DHA-S injection in normal and pathological pregnancies encouraged us to apply this idea to a new modified dynamic test of feto-placental function: **"A betamethasone suppression DHA-S-loading Test".**

The estrogen response pattern following betamethasone application changes with the condition of the fetus. **A healthy, normal fetus reacts with a more intense decrease of estrogens than a fetus at risk and the return to values before injection is more rapid.**

In cases of a "normal response" the decline of E_3 three hours after intravenous injection of 8 mg betamethasone exceeds 50% of preinjection values.
In pathological pregnancies the decline of the primarily low estrogen levels is less distinct and the return to basal values is slower.
With an additional application of 50 mg DHA-S three hours after betamethasone injection to the mother and determination of maternal plasma estrogens in short intervals there might be the possibility of a new functional method determining placental function: "An inhibition test of the fetal pituitary-adrenal axis combined with a loading-test of the placenta.".
This test could evaluate the **condition of the fetus by determination of E_3 after betamethasone application** to the mother and could also clarify the **reserve capacity of the placenta following DHA-S loading** in a state of maximal suppression of the endogenous estrogen-precursors **by determination of E_2** (Fig. 9).
The following conclusions can be drawn from our investigations:

1. The changes of plasma and urinary estrogens depend on the dose of betamethasone and on the way of application.
2. The maximal decrease of maternal E_2 and E_3 is reached three hours after injection. The return to preinjection values takes more than 4–5 days.
3. The decline of estrogens following betamethasone injection to the mother is causes by suppression of adrenocortical estrogen-precursors mainly derived from the fetus.
4. The changes of maternal plasma estrogens after betamethasone and subsequent DHA-S loading offer new possibilities for testing the fetoplacental unit.

Keywords: DHA-S-loading test, dynamic functional test, feto-placental unit, placental insufficiency

Zusammenfassung

Der Einfluß von Betamethason auf die fetoplazentare Einheit.
In unserer Studie soll der Einfluß von Betamethason auf die Oestrogen-Biosynthese in Fet und Plazenta untersucht werden. **Weiterhin wollen wir herausfinden, ob Veränderungen der mütterlichen Östrogenkonzentration im Plasma nach Verabreichung von Betamethason an die Mutter als ein neuer, dynamischer funktioneller Test für Fet und Plazenta herangezogen werden können.** Ebenso war vorgesehen, die Plazenta durch DHA-S- Belastung zu testen, nachdem die fetale Hypophysen-Nebennierenrindenachse durch Betamethason supprimiert wurde.
Die mütterlichen **Plasma-Spiegel von Östron (E_1), Östradiol 17-β (E_2), Östriol (E_3), Cortisol und die Gesamt-Östrogene im 24-h-Urin** wurden bei normalen und pathologischen Schwangerschaften im 3. Trimenon bestimmt.

Die Gesamtzahl von 32 Patientinnen wurde in 7 Gruppen unterteilt.
Die Gruppen I, II und III erhielten 12 mg Betamethason i.m. oder 8 mg i.v. Die Gruppen IV, V, VI, VII erhielten Betamethason und zusätzlich 25 oder 50 mg DHA-S i.v. Mütterliches Venenblut für die Bestimmungen von E_1, E_2, E_3 und Cortisol wurden vor der Injektion von Betamethason und in kurzen Zeitabständen während des 1. Behandlungstages (genaue Zeitabstände bitte den Abbildungen entnehmen) sowie 1 Stunde nach der 2. Injektion am Tag II in der Gruppe I und II abgenommen. Eine Probe wurde jeweils an den 6 folgenden Tagen um 9.00 h entnommen.

E_1, E_2 und E_3 wurden radioimmunologisch bestimmt, die Gesamtöstrogene im Urin wurden photometrisch gemessen. Freies Cortisol wurde nach der Methode von Murphy bestimmt.
Die Basalwerte von E_1, E_2 und E_3 im mütterlichen Plasma waren bei normalen Schwangerschaften signifikant höher, als bei pathologischen Fällen (Abb. 1, 2, 3, 4).
Der Abfall der Plasma-Östrogene, Cortisol und der Gesamtöstrogene im Urin ist dosisabhängig und erreicht ein Maximum nach der 2. Betamethason-Injektion (Abb. 1, 2, 3).

Die Untersuchungen der Verlaufskurven für die Plasma-Östrogene nach Betamethason zeigen einen großen Unterschied zwischen normalen und pathologischen Schwangerschaften. **Der Abfall von Östradiol drei Stunden nach intramuskulärer Injektion von Betamethason betrug 69% bei normalen, im Vergleich zu 33% bei pathologischen Fällen.** Der Abfall von E_3 war bei normalen Schwangerschaften ebenfalls ausgeprägter als bei komplizierten Fällen (63 gegen 42%) (Abb. 1 und 2).
Die Östrogenwerte erreichten bei normalen Schwangerschaften den Basalwert nicht vor 3 Tagen nach der Injektion im Gegensatz zu 5 Tagen bei pathologischen Fällen.
Gemäß den Ergebnissen, die wir bei den Patienten-Gruppen IV, V und VI erhalten haben, **sind die Anstiege von E_2 und E_3 30 Minuten nach DHA-S-Injektion bei normalen Schwangerschaften höher als bei pathologischen Fällen** (Abb. 5 und 6).
Die unterschiedlichen Kurvenverläufe von E_2, E_3 und der Urin-Östrogene nach Betamethason-Injektionen bei normalen und pathologischen Schwangerschaften veranlaßten uns, einen neuartigen, modifizierten, dynamischen Test für die Beurteilung der fetoplazentaren Funktion vorzuschlagen: „den **Betamethason-Suppressions-DHA-S-Belastungstest!**"
Das Antwortmuster der Östrogene nach Betamethason-Verabreichung verändert sich mit dem Zustand des Feten. **Ein gesunder, normaler Fet reagiert mit einem stärkeren Abfall der Östrogene, als ein vorgeschädigter Fet und das Wiederaufsteigen zu den Basalwerten geschieht schneller.** Bei Fällen mit einer normalen Antwort übersteigt der Abfall von E_3 – 3 Stunden nach intravenöser Injektion von 8 mg Betamethason – 50% des Basalwertes.
Bei pathologischen Schwangerschaften ist der Abfall der schon primär niedrigen Östrogenwerte weniger ausgeprägt und die Rückkehr zu den Basalwerten langsamer. Mit zusätzlicher Verabreichung von 50 mg DHA-S, 3 Std. nach Betamethasongabe an die Mutter und Bestimmung der mütterlichen Plasma-Östrogene in kurzen Zeitabständen, könnte sich ein Weg zu einem neuen, funktionellen Test

für die Beurteilung der Plazenta-Funktion ergeben: Ein Hemmungstest der fetalen Hypophysen-Nebennierenrindenachse kombiniert mit einem Belastungstest für die Plazenta. Dieser Test könnte durch die **E_3-Bestimmung nach Betamethason-Verabreichung an die Mutter Auskunft über den Zustand des Feten** geben und zudem die **Reserve-Kapazität der Plazenta nach DHA-S-Belastung durch die Bestimmung von E_2** beurteilen. In diesem Zustand ist nämlich die Produktion der endogenen Östrogen-Präkursoren maximal supprimiert (Abb. 9).
Folgende Schlußfolgerungen können aus unseren Untersuchungen gezogen werden:

1. Die Veränderungen der Plasma- und Urin-Östrogene sind abhängig von der Betamethason-Dosis und der Verabreichungsform.
2. Der maximale Abfall von mütterlichem E_2 und E_3 wird drei Stunden nach der Injektion erreicht. Die Rückkehr zu Basalwerten erfolgt erst nach vier bis fünf Tagen.
3. Der Abfall der Östrogene nach Betamethason-Injektion an die Mutter entsteht hauptsächlich durch die Suppression der adreno-corticalen Östrogenpräkursoren, die vom Feten stammen.
4. Die Veränderungen der mütterlichen Plasma-Östrogene nach Betamethason und nachfolgender DHA-S-Belastung zeigen neue Wege auf, den Zustand der feto-plazentaren Einheit beurteilen zu können.

Schlüsselwörter: DHA-S-Belastungstest, dynamischer Plazentafunktionstest, fetoplazentare Einheit, Plazentarinsuffizienz.

Résumé

Influence de la bétaméthasone sur l'unité foeto'placentaire

Dans le présent article nous avons examiné l'influence de bétaméthasone sur la biosynthèse des oestrogènes dans le placenta et le foetus. De plus, **nous avons cherché à savoir si des modifications des concentrations d'oestrogènes dans le plasma après administration de bétaméthasone à la mère pourraient être utilisées comme un nouveau test fonctionnel et dynamique du placenta et du foetus.** Nous avons essayé aussi de tester par charge DHA-S la fonction stéroidobiogénétique du placenta après la suppression de l'axe hypophiso-adrenocortical par bétaméthasone.
A cet effet, **nous avons déterminé les concentrations plasmatiques maternelles de l'oestrone (OE_1), de l'oestradiol (OE_2), de l'oestriol (OE_3), du cortisol et celles des oestrogènes de l'urine de 24 heures** au troisième trimestre de grossesses normales et pathologiques. Les 32 parturientes examinées ont été réparties en VII groupes. Les groupes I, II et III ont reçu 12 mg ou 8 mg de bétaméthasone i.m
Les groupes IV, V, VI et VII ont reçu la bétaméthasene et aussi 25 mg ou 50 mg de DHA-S i.v.
L'OE_1, l'OE_2 et l'OE_3 ainsi que le cortisol ont été déterminés dans le sang veineux avant l'injection de bétaméthasone et à courts intervalles pendant la première journée du traitement (cf. les graphiques pour les temps précis) et une heure après la seconde injection au deuxième jour dans les cas des groupes I et II.
Un prélèvement a été effectué à 9 h. du matin chacun des six jours suivants. L'OE_1, l'OE_2 et l'OE_3 plasmiques ont été définis par la méthode radioimmunologique et les oestrogènes totaux urinaires par méthode photométrique.

Le cortisol non-conjugué a été déterminé par la méthode de MURPHY.
Les concentrations d'OE_1, d'OE_2 et d'OE_3 en plasma maternel avant l'injection de bétaméthasone ont été considérablement plus élevées dans les grossesses normales que dans celles pathologiques (fig. 1, 2, 3, 4).
La baisse des oestrogènes plasmatiques, du cortisol et des oestrogènes urinaires dépend de la dose et atteint un maximum après la seconde injection de bétaméthasone (fig. 1, 2, 3). Les investigations des changements des oestrogènes plasmatiques après bétaméthasone montrent une grande différence entre les grossesses normales et pathologiques. **La baisse d'OE_2 trois heures après l'injection intramusculaire de bétaméthasone a atteint 69% dans les grossesses normales et seulement 33% dans les grossesses pathologiques'** La baisse d'OE_3 a été également plus importante dans les cas normaux (63%) que dans les cas compliqués (42%) (fig. 1 et 2).

Les valeurs des oestrogènes en grossesse normale ont retrouvé leur niveau de départ trois jours seulement après l'injection et même 5 jours pour les grosses pathologiques. Selon les résultats des patientes des groupes IV, V et VI, **les hausses d'OE_2 et d'OE_3 plasmiques 30 minutes après l'injection de DHA-S sont plus grandes en grossesse normale qu'en grossesse pathologique.** (fig. 5 et 6).

La différence des courbes des concentrations plasmiques d'OE_2, d'OE_3 et des oestrogènes urinaires après l'injection de bétaméthasone et de DHA-S entre les grossesses normales et pathologiques nous a incités à appliquer cette idée comme un nouveau test dynamique de la fonction foeto-placentaire: **«Un test d'inhibition par bétaméthasone et de stimulation par DHA-S».**

La réaction des oestrogènes après l'injection de bétaméthasone varie selon la condition du foetus. **Un foetus normal et sain réagit par une baisse plus forte des oestrogènes qu'un foetus «à risque» et le retour aux valeurs de base (c.à.d. précédant l'injection) est plus rapide.**

Dans les cas d'une «réaction normale», la baisse d'OE_3 trois heures après l'injection intraveineuse de 8 mg de bétaméthasone dépasse 50% des valeurs initiales. **Dans les cas des grossesses pathologiques la baisse des valeurs initialement basses des oestrogènes est moins prononcée et le retour aux valeurs de base est plus lent.**

L'injection supplémentaire de 50 mg de DHA-S trois heures après l'injection de bétaméthasone à la mère et la détermination des oestrogènes plasmatiques maternels à courts intervalles pourrait nous donner la possibilité d'appliquer une nouvelle méthode pour définir la fonction placentaire: «Un test d'inhibition de l'axe hypophiso-adrenocortical combiné avec un loading-test» du placenta.

Ce test pourrait permettre d'évaluer **la condition du foetus en déterminant l'OE_3 après l'injection de bétaméthasone** à la mère ainsi que **la capacité de réserve placentaire après l'administration de DHA-S** au moment de la suppression maximale des précurseurs endogènes des oestrogènes **par détermination d'OE_2** (fig. 9). Les résultats obtenus nous ont permis de tirer les conclusions suivantes:

1. Les variations des oestrogènes plasmatiques et urinaires dépendent de la dose et de la manière d'application de la bétaméthasone.
2. La baisse maximale de l'OE_2 et de l'OE_3 maternels plasmatiques est obtenue trois heures après l'injection. Le retour aux valeurs initiales dure plus de 4–5 jours.
3. La baisse des oestrogènes suivant l'injection de bétaméthasone résulte de la suppression des précurseurs adrénocorticals des oestrogènes, principalement produits par le foetus.
4. Les variations des oestrogènes plasmatiques maternels après l'injection de bétaméthasone et de DHA-S nous offre des nouvelles perspectives pour tester l'unité foeto-placentaire.

Mots-clés: DHA-S-«loading-test», insufficance placentaire, test fonctionnel dynamique, unité foeto-placentaire.

Bibliography

[1] ARAI, K., Y. KUWABARA, S. OKINAGA: The effect of adrenocorticotropic hormone and dexamethasone, administered to the fetus in utero, upon maternal and fetal estrogens. Amer. J. Obstet. Gynecol. 113 (1972) 316

[2] BROWN, B. J., H. A. GABERT, M. A. STENCHEVER: Respiratory distress syndrome, surfactant biochemistry, and acceleration of fetal lung maturity: a review. Obstet. Gynecol. Surv. 36 (1975) 71

[3] BUSTER, J. E., G. E. ABRAHAM, F. W. KYLE, J. R. MARSHALL: Serum Steroid Levels Following a Large Intravenous Dose of Steroid Sulfate Precursor During the Second Trimester of Human Pregnancy. I. Dehydroepiandrosteron Sulfate. J. Clin. Endocrinol. Metab. 38 (1974) 1031

[4] CHALLIS, J. R. G., I. J. DAVIES, K. BENIRSCHKE, A. G. HENDRICKX, K. J. RYAN: The Effects of Dexamethasone on the Peripheral Plasma Concentration of Androstendione, Testosterone and Cortisol in the Pregnant Rhesus Monkey. Endocrinology 96 (1975) 185

[5] CHARLES, D., J. L. PINKUS, R. FANOUS, S. C. CHATTORAI: The effect of Dexamethasone on the urinary excretion of steroid during pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 78 (1971) 241

[6] CRIMAIL, Ph., G. DAUPTAIN: Vers une therapeutique preventive de la maladie des membranes hyalines. Rev. franc. Gynec. 70 (1975) 497

[7] DICZFALUSY, E.: Endocrine function of the human fetus and placenta. Amer. J. Obstet. Gynecol. 119 (1974) 419

[8] GENNSER, G., S. OHRLANDER, P. ENEROTH: Cortisol in amniotic fluid and cord blood in relation to prenatal betamethason load and delivery. Amer. J. Obstet. Gynecol. 124 (1976) 43

[9] ISHERWOOD, D. M., R. E. OAKEY: Control of estrogen production in human pregnancy: effect of trophic hormones on steroid biosynthesis by the foetal adrenal gland in vitro. J. Endocrinol. 68 (1976) 321

[10] KLOPPER, A., V. JANDIAL: The conversion of dehydroepiandrosteron to estrogen – a dynamic placental function test. Excerpta Medica 5 (1975) 93

[11] LAURITZEN, CH.: A clinical test for placental functional activity, using DHEA-S-Sulfate and ACTH-injections in pregnant women. Acta Endocrinol. 119 (1967) 88

[12] LAURITZEN, CH., W. D. LEHMANN: Levels of chorionic gonadotrophin in the newborn infant and their relationship to adrenal dehydroepiandrosterone. J. Endocrinol. 39 (1967) 173

[13] LAURITZEN, CH., J. R. STRECKER, W. D. LEHMANN: Dynamic tests of placental function. Some findings on the conversion of DHA-S to estrogens. In: KLOPPER, A.: Oestrogens in Plasma, Churchill-Livingstone, London 1976

[14] LEHMANN, W. D., J. MISINGER, CH. LAURITZEN: Umwandlungsrate von (Δ-^{14}C) Dehydroepiandrosteon in Oestron und Oestradiol-17β durch normale sowie Gestose- und Diabetes-Placenten. Arch. Gynäkol. 210 (1971) 49

[15] LEHMANN, W. D., J. R. STRECKER: Oestrogens in maternal Plasma following Intraamnial Injection of (^{3}H)-Dehydroepiandrosteron-Sulfat in Midpregnancy. J. Perinat. Med. 4 (1976) 255

[16] MURPHY, B. E. P.: Some studies on the protein binding of steroid and their applications to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. J. clin. Endocrinol. 27 (1967) 973

[17] NEGULESCU, R. I., J. R. STRECKER, CH. LAURITZEN: Der Einfluß von Betamethason auf die fetoplacentare Einheit. Unpublished results 1976

[18] OHRLANDER, S., G. GENNSER, L. GRENNERT: Impact of betamethason load given to pregnant women on endocrine balance of fetoplacental unit. Amer. J. Obstet. Gynecol. 123 (1975) 228

[19] SCHWENZEL, W., H. JUNG, H. LAHMANN, E. ETZRODT, C. STICHERLING, K. KORZ, B. LIEDTKE, H. CHANTRAINE: Erste Erfahrungen mit der praenatalen Beeinflussung der kindlichen Lungenreife durch Betamethason. Z. Geburtshilfe Perinatol. 179 (1975) 45

[20] SCHWENZEL, W., H. JUNG: Pränatale Behandlungsmethoden zur Vermeidung eines Atemnotsyndroms bei frühgeborenen Kindern. Gynäkologe 8 (1975) 198

[21] SIEBERT, W., C. MEITINGER: Prophylaxe des Atemnotsyndroms mit Betamethason. Geburtshilfe Frauenheilk. 35 (1975) 130

[22] SIITERI, P., P. C. MACDONALD: Placental Estrogen Biosynthesis During Human Pregnancy. J. Clin. Endocrinol. Metab. 26 (1966) 751
[23] SIMMER, H. H., MARJORIE FRANKLAND, MARGARET GREIPEL: On the regulation of fetal and maternal 16 Alpha-hydroxy-dehydroepiandrosterone and its sulfate by cortisol and ACTH in human pregnancy at term. Amer. J. Obstet. Gynec. 121 (1975) 646
[24] SIMMER, H. H., D. TULCHINSKY, E. M. GOLD, MARJORIE FRANKLAND, MARGARET GREIPEL, ANITA S. GOLD: On the regulation of estrogen production by cortisol and ACTH in human pregnancy at term. Amer. J. Obstet. Gynec. 119 (1974) 283
[25] STRECKER, J. R., CH. LAURITZEN: DHA-S-Belastungstest zur Beurteilung der Plazentafunktion mit radioimmunologischer Bestimmung der Plasma-Oestrogene. Z. Geburtshilfe Perinatol. 178 (1974) 254
[26] STRECKER, J. R., CH. LAURITZEN: Injection of Dehydroepiandrosterone Sulfate, ACTH, HCG and Prostaglandin into the Amniotic Fluid and the Fetus during Midpregnancy legal Abortion. Influence on Maternal Plasma Oestrogens, Testosterone, HCG, HPL and Prolactin. Hormone Metab. Res. In press 1976
[27] TAEUSCH, H. W., jr.: Glucocorticoid prophylaxis for respiratory distress syndrome: A review of potential toxicity. J. Pediat. 87 (1975) 617
[28] TOMBY RAJA, R. L., A. C. TURNBULL: Prediactive Oestradiol Surge of Premature Labour and its Suppression by Glucocorticoids. Aust. N.Z.J. Obstet. Gynaec. 15 (1975) 191
[29] TOWNSLEY, J. D.: Utilisation of dehydroepiandrosteron and its sulphate for oestrogen production by pregnant baboons. Acta Endocrinol. 81 (1976) 830
[30] TULCHINSKY, D.: The value of estrogen assays in obstetric disease. In: A. KLOPPER, "Oestrogens in Plasma". Edit. Churchill-Livingstone, London 1976.
[31] WINTOUR, E. M., E. H. BROWN, D. A. DENTON, K. J. HARDY, J. G. MCDOUGALL, C. J. ODDIE, G. T. WHIPP: The Ontogeny and Regulation of Corticosteroid secretion by the Ovine Foetal Adrenal. Acta Endocrinol. 79 (1975) 301
[32] YLIKORKALA, O., R. TUIMALA: Effect of dexamethasone on serum levels of human placental lactogen during the last trimester of pregnancy. J. Obstet. Gynaec. Brit. Cwlth.

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