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A critical period in the onset of parturition in rats and uterine sensitivity to estradiol and progesterone

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Summary. The purpose of this paper was to impair normal parturition in rats in order to measure tissue levels of progestins and estrogens and compare these results with those of normal parturition in rats. Abnormal parturition was obtained by injection of isotonic saline into the uterine lumen of pregnant rats at the end of pregnancy or by handling the uterus. After each of these treatments on day 21 of pregnancy, parturition was impaired in 70 to 98 % of the rats. When the treatments were carried out earlier or later in pregnancy, there was little or no impairment. Our results indicate transient discrepancies in plasma and tissue levels of steroids 6 h after treatment on day 21: 20 α-HP concentrations increased in treated rats compared to controls (uteri : + 470 % ; $p < 0.01$; ovaries : + 89 % ; $p < 0.001$) ; concomitantly, there was a sharp rise in P concentrations in uteri (+ 74 % : $p < 0.05$) and ovaries (+ 52 % ; $p < 0.05$). Inversely, uterine concentrations of E_2 decreased 6 h after treatment compared to controls (− 30 % ; $p < 0.05$), although there was a transient rise of E_2 in the ovaries (+ 30 % ; $p < 0.05$).

Twenty-four hours later, E_2 concentrations were always lower in the uteri (− 30 % ; $p < 0.01$). No change in E_1 levels was noted in the uteri or ovaries of either the control or treated rats. The physiological significance of these changes and their consequences on uterine reactivity at term have been discussed. The data demonstrate that day 21 was a critical period in the parturient activity of the rat uterus which appears to be primarily affected by uterine levels of E_2 between days 21 and 22 of pregnancy.

Introduction.

In pregnant rat, there is good evidence that a change in the ratio of progesterone to estrogen is implicated in uterine reactivity near term. Dukes *et al.* (1974) postulated that during the last 48 h of pregnancy, changes in preparation for parturition could be divided into two successive phases, the first involving luteolysis with a decrease in plasma and uterine concentrations of progesterone between days 19 and 23 of pregnancy (Hashimoto *et al.*, 1968 ; Wiest, 1970 ; Egg *et al.*, 1974 ; Ichikawa *et al.*, 1974 ; Sanyal, 1978) and the second an estrogen-dependent phase beginning when the concentration of progesterone falls below a critical level and that of estrogens attains a critical threshold. Yoshinaga *et al.*, (1969), Shaikh (1971), Waynforth *et al.*, (1972) and Shaikh *et al.*, (1977) showed that estrogen concentration in ovarian venous plasma rises

sharply from day 21. Some works studying the relevance of these changes in steroid hormone concentrations to parturient activity of the uterus, have focused on the effect on the uterus of interactions between ovarian steroids and catecholamines (norepinephrine or epinephrine) (Maltier and Cavaillé, 1978 ; Maltier *et al.,* 1980).

We have shown previously (Maltier and Cavaillé, 1975) that isotonic saline injection into the uterine lumen seriously impairs parturition when performed on day 21 *post coitum.* Handling the uterus at the same stage of pregnancy also results in abnormal delivery, indicating that day 21 of pregnancy is a critical period in the onset of parturition in rat (Maltier and Cavaillé, 1975). A change in the balance of uterine epinephrine and norepinephrine has been previously reported by Maltier and Cavaillé (1975) in association with these abnormal deliveries. The impairment observed after both treatments was similar to that described after ovariectomy (delayed parturition, partial delivery or no delivery ; Csapo and Wiest, 1969), suggesting that some disorders in ovarian steroids might be implicated in abnormal parturition.

The aim of the present paper was to compare plasma and tissue levels of progesterone (P), 20α-dihydroprogesterone (20α-HP) and estrogens (E_1 and E_2) in rats with normal and abnormal parturition. The changes in hormonal levels accompanying abnormal delivery seemed to make our experimental rats excellent models for studying the chronology and localization of some endocrine events occurring in pregnant rat near term.

Material and methods.

Animals and treatments. — Primiparous Sprague-Dawley rats were used. They were fed with commercial laboratory chow (UAR B03). Female rats in groups of five per cage were kept under constant temperature (23 °C) and a lighting schedule of 14 h of light and 10 h of dark. One male was put into each of the cages for one night. Fourteen days later, the pregnant rats were screened by palpation. Fertilization was assumed to have occurred between 2 and 6 a.m., and this time was taken as day 1 of pregnancy.

Group 1. — At 10 a.m. on day 19, 20, 21 or 22 of pregnancy, the females were laparotomized under ether anesthesia and gently injected through each uterine horn with 0.5 ml of isotonic saline, according to the procedure of Maltier and Cavaillé, (1975). Immediately after injection, the uterine horns were replaced in the abdomen. Half the animals treated at 10 a.m. on day 21 were sacrificed 6, 24 or 48 h later for blood and organ collection ; the remaining rats were used to control delivery.

Group 2. — At 10 a.m. on day 21, the uterus was exposed and handled but no saline was injected. The uterine horns were then immediately replaced in the abdomen. The animals were sacrificed 6 h later for blood and tissue collection or were used to check the timing and process of delivery.

Group 3. — At 10 a.m. on day 21, the rats were anesthetized with ether and the abdomen opened without handling the uterus. All these rats were used to control hormonal levels and parturition.

Group 4. — At 10 a.m. on day 21 of pregnancy, the rats were treated the same way as the females of group 1 and then immediately given s.c. either 3 µg of estradiol dipropionate (Roussel-Uclaf) in 0.5 ml of olive oil or the vehicle alone. All these rats were allowed to deliver spontaneously.

Group 5. — The females were left intact and used to control parturition. Those in all groups used for control of delivery were autopsied after 12 noon on day 23 to determine if parturition was complete or partial.

Enzyme assays. — The rats were killed by cervical dislocation and their ovaries immediately isolated and frozen in liquid nitrogen before enzyme assay. Ovarian tissues were analyzed biochemically for Δ5-3β and 20α-hydroxysteroid dehydrogenase (OHSDH) by methods previously described by Wilcox and Wiest (1966) and Kuhn and Briley (1970) and then applied by Lacy *et al.,* (1976).

Δ5-3β-OHSDH. — The ovaries were homogenized in 1.5 ml of 0.25 M sucrose at 0 °C. The homogenate was centrifuged for 30 min at 85 000 × g. The supernatant was taken for assay of Δ5-3β-OHSDH. The standard reaction mixture was glycine (40 µmol) NaOH buffer, pH 9.4, containing NAD^+ (0.3 µmol), nicotinamide (10 µmol) and supernatant (150 µl) in a final volume of 750 µl. The extinction change was measured in a spectrophotometer (Beckman DBT) at 340 mµ before and after the addition of 50 µl of ethanolic pregnenolone (0.1 ng/ml). Rates were proportional to amounts of enzyme and dependent on added NAD^+.

20α-OHSDH. — The ovaries were homogenized in Tris-HCl buffer 0.1 M, pH 7.4 (30 µl of buffer/mg of ovary), containing cysteine (1 mM), EDTA (1 mM) and nicotinamide (10 mM). The homogenate was centrifuged for 30 min at 20 000 × g and the supernatant was used for the assay of 20α-OHSDH. The standard reaction mixture was Tris-HCl-cysteine buffer, pH 8, $NADP^+$ (0.5 µmol) and supernatant (200 µl) in a final volume of 750 µl. The extinction change was measured in a spectrophotometer (Beckman DBT) at 340 mµ before and after the reaction was initiated with 50 µl of ethanolic 20α-HP (0.1 mg/ml). Rates were dependent on enzyme and $NADP^+$.

Steroid assays. — Steroid determinations were obtained by radioimmunological assays of uterine and plasma samples during the last 3 days of pregnancy in treated and control rats (groups 1, 2 and 3). Blood was collected under ether anesthesia. Uterine blood was obtained at the cervical portion of the vein after ligation of its ovarian end. Peripheral blood was drawn from the aorta into a heparinized syringe. All blood samples were collected in heparinized flasks and then centrifuged at 1 500 × g for 15 min at 0 °C ; the plasma was immediately processed for RIA. Ovaries and uteri were rapidly isolated, weighed and frozen in liquid nitrogen until steroid analysis. The procedures used in RIA were carried out according to methods described by Castanier and Scholler (1970), Florensa and Sommerville (1973) and Abraham (1974). [1,2,-(n)-^{3}H] P (49 Ci/mmol ; Radiochemical Centre, Amersham, England) ; [1,2,-(n)-^{3}H] 20α-HP (40 Ci/mmol ; New England Nuclear GmbH, West Germany) ; [2,4,6,7-^{3}H] E_1 (55 Ci/mmol ; Radiochemical Centre, Amersham, England) and [2,4,6,7-^{3}H] E_2 (108 Ci/mmol ; Radiochemical Centre, Amersham, England) were purified by

column chromatography before use. The P antiserum (anti-progesterone-11α [succinyl] -bovine serum albumin), used at a final dilution of 1:3 000, had no significant cross-reactivity with 20α-HP (1 %), 5α-pregnan-3,20-dione (2.5 %), 5β-pregnan-3,20-dione (2 %) or deoxycorticosterone (3.5 %). The 20α-HP antiserum (anti-20α-hydroxy-4-pregnen-3-one-3 [0-carboxymethyl-oxime] -bovine serum albumin), a gift of Endocrine Sciences (Tarzana, California), was used at a final dilution of 1:3 000 ; this antibody had a cross-reactivity of 10 % with 20β-HP but no significant cross-reactivity (< 0.3 %) with any of the other steroids. E_1 (or E_2) antiserum, obtained from rabbits after immunization with E_1-17 carboxymethyl-oxime-serum albumin conjugate, was used at a final dilution of 1:30 000 ; this antiserum had a cross-reactivity of 4 % with estriol and no significant cross-reactivity (< 0.1 %) with cortisol, androgens or progestins. The standard curves of the assay ranged linearly between 0 and 600 pg per assay tube for progestins and between 0 and 160 pg per assay tube for estrogens.

We extracted duplicate samples twice with 4 ml of diethyl ether (Merck ; diethyl ether dried GR) ; about 1 000 cpm of radioactive steroids had been added to these for estimation of procedural loss.

Sample residues, dissolved in 100 μl of solvent, were applied to 0.6 × 5-cm Sephadex LH-20 columns with benzene-ethanol (85:15) as solvent for E_1 and E_2 and to 0.6 × 17-cm Sephadex LH-20 columns with benzene-methanol (95:5) as solvent for P and 20α-HP. Steroid recovery was determined in the extracts by scintillation spectrometry (Isocap 3000, Nuclear Chicago). Recovery (mean ± SEM) was 89 ± 3.2 % for P, 88 ± 4.5 % for 20α-HP, 84 ± 7.3 % for E_1 and 86 ± 13.7 % for E_2. The extracts for progestin determination were incubated for 30 min at 37 °C with 2 500 cpm [^{3}H] P or [^{3}H] 20α-HP and P or 20α-HP antiserum. For estrogen determination, the extracts were incubated for 30 min at 37 °C with 4 000 cpm of radioactive steroid and E_1 or E_2 antiserum. Bound radioactive steroid was determined after removal of unbound steroid according to the procedure of Castanier and Scholler (1970).

Assay sensitivity was 0.2 ng/ml for P and 0.05 ng/ml for 20α-HP, E_1 and E_2. The intra-assay coefficient of variation was 6.7 % for P, 6.5 % for 20α-HP, 7 % for E_1 and E_2. The interassay coefficient of variation was 11.6 % for P, 13.8 % for 20α-HP and 14 % for E_1 and E_2.

Statistical methods. — The results were analyzed statistically using Student's t-test. A difference was considered statistically significant when double-tailed p was < 0.05.

Results.

In control and untreated Sprague-Dawley rats (groups 3 and 5), parturition normally occurred between 12 noon on day 22 and 12 noon on day 23 of pregnancy (fig. 1). After injections of intra-uterine isotonic saline at 10 a.m. on day 21 (fig. 1), 2 % of the rats had completely normal delivery and 42 % entirely suppressed delivery, the whole litter remaining in the uterus after 12 noon on day 23 and resulting in the death of the dam ; 49 % of the rats had partial delivery,

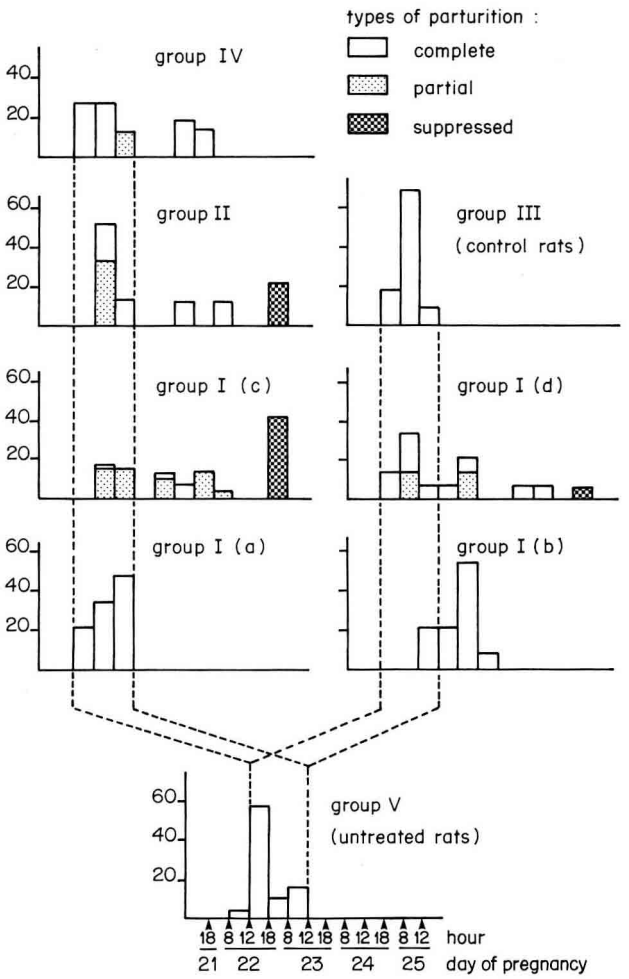

FIG. 1. — *The timing and process of parturition in control and treated rats.*
Group 1. Rats were treated with an intrauterine injection of saline at 10 a.m. on day 19 (a), day 20 (b), day 21 (c) or day 22 (d) of pregnancy. *Group 2.* Rats were laparotomized and their uterine horns exposed and handled at 10 a.m. on day 21. *Group 3.* Rats were laparotomized at 10 a.m. on day 21 without handling the uterus. *Group 4.* Rats were injected i.u. with isotonic saline at 10 a.m. on day 21 and received 3 µg of estradiol dipropionate. *Group 5.* Untreated rats. Parturition normally occurred between 12 noon on day 22 and 12 noon on day 23 of pregnancy (dashed lines).

some fetuses remaining in the uterus after 12 noon on day 23. Parturition was complete but delayed in 7 % of the rats. After laparotomy and handling of the uterus, we noted analogous, though less severe, consequences (fig. 1). The administration of estradiol dipropionate at 10 a.m. on day 21 immediately after isotonic saline resulted in a high proportion of complete deliveries (88 %), partial deliveries (12 %) occurring at the normal time (fig. 1). Moreover, in this group of animals, we never observed suppressed parturition. Ether anesthesia and

laparotomy without handling the uterine horns had no effect on parturition (fig. 1). After injection of intrauterine isotonic saline at 10 a.m. on day 19, all deliveries were normal ; after injection at 10 a.m. on day 20 or 22, we noted less severe consequences than after injection at 10 a.m. on day 21 (fig. 1).

P concentrations (fig. 2). — At 4 p.m. on day 21, *i.e.* 6 h after saline injection, uterine P concentration increased compared to control rats (+ 74 % ; $p < 0.05$). The same results were noted after handling the uterus since the P level was 83.2 ± 16.9 ng/g with no significant difference between either group of treated rats. These changes appeared concomitantly with a similar increase of

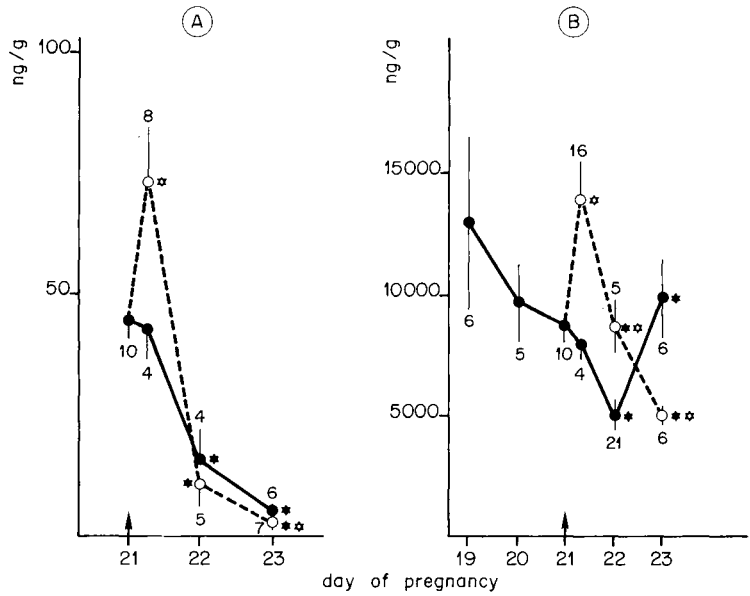

FIG. 2. — *Progesterone* (P) *concentrations in control* (•—•) *and isotonic* NaCl-*treated* (o---o) *rats.* The means ± SEM are indicated. The ciphers on the figure are the numbers of animals.
A : uterus, B : ovaries.
☆ : significantly different from values in control rats ($p < 0.05$).
★ : significantly different from values at previous stage of pregnancy ($p < 0.05$).
— : The arrow indicate the time of injection.

ovarian P concentrations after saline injection (+ 52 % ; $p < 0.05$) or handling the uterus (13 253 ± 2 418 ng/g). This elevation was not correlated with a change in ovarian Δ_5-3β-OHSDH (table 1). Within 24-48 h after treatment, *i.e.* at 10 a.m. on day 22 or 23 of pregnancy, uterine P concentrations decreased to within a normal or subnormal range ; on day 23, a decrease in ovarian P concentration was noted (− 47 % ; $p < 0.05$), associated with a decline in Δ_5-3β-OHSDH activity (table 1). In contrast, ovarian P concentrations of normal control rats rose near term (+ 96 % ; $p < 0.05$) concomitantly with higher ovarian Δ_5-3β-OHSDH activity (table 1).

TABLE 1

Δ_5-3β and 20α-OHSDH activities in control and saline-treated rats (means ± SEM)

Day of pregnancy	Δ_5-3β-OHSDH (mU/mg ovary)		20α-OHSDH (mU/mg ovary)	
	Control rats	Treated rats	Control rats	Treated rats
19	0.62 ± 0.06 (8)	—	0.93 ± 0.09 (8)	—
20	0.57 ± 0.04 (5)	—	1.67 ± 0.12★ (6)	—
21	0.74 ± 0.10 (9)	0.91 ± 0.11 (6)	2.10 ± 0.36 (5)	1.47 ± 0.09 (9)
22	1.00 ± 0.15 (9)	0.86 ± 0.18 (6)	1.07 ± 0.11★ (14)	2.28 ± 0.35★☆ (6)
23	1.89 ± 0.27★ (8)	0.36 ± 0.04★☆ (4)	1.98 ± 0.25★ (8)	2.58 ± 0.09☆ (5)

The number of animals is shown in parentheses.
☆ : significantly different from values in control rats ($p < 0.05$).
★ : significantly different from values at previous stage of pregnancy ($p < 0.05$).

20α-HP concentrations (fig. 3). Six hours after i.u. isotonic saline, uterine 20α-HP concentrations increased sharply (+ 470 % ; $p < 0.01$) ; in this group, the hormone levels were closely similar to those measured after the uterus was handled (26.7 ± 12.3 ng/g). Concomitantly, we noted a rapid increase in 20α-HP concentrations in ovaries (+ 89 % ; $p < 0.001$) of saline-treated rats as well as in rats whose uterus had been handled (6 508 ± 441 ng/g).

As shown in table 1, this ovarian increase in 20α-HP concentrations was not a result of higher 20α-OHSDH activity. Later, *i.e.* at 10 a.m. on day 23, while ovarian 20α-HP concentrations decreased sharply compared to control rats (− 79 % ; $p < 0.05$), hormone levels in the uterus were within the normal range of the control rats.

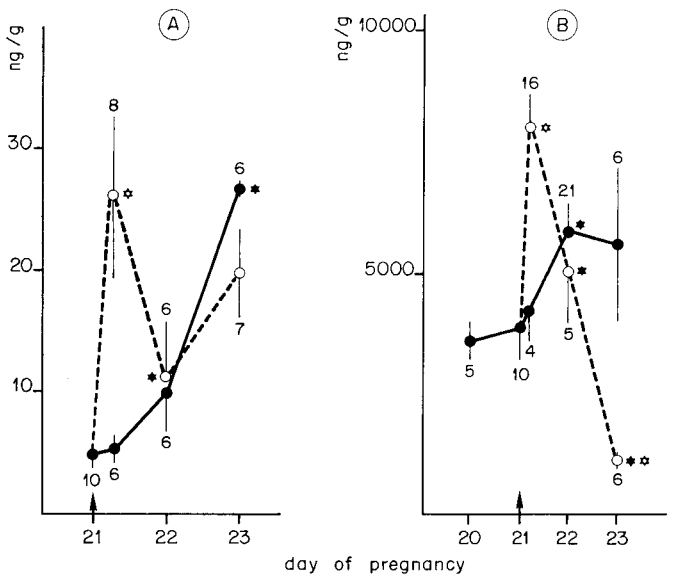

FIG. 3. — *20α-hydroxy-4-pregnen-3-one* (20α-HP) *concentrations in control* (•——•) *and isotonic* NaCl-*treated* (o---o) *rats.* See legend of figure 2.

Estrogen concentrations. — Figure 4 shows changes in mean E_2 concentrations in the uteri, plasma and ovaries of control and treated pregnant rats. Within the last 2 days of pregnancy, the concentrations of E_2 in control rats increased in the uteri and plasma. Between days 21 and 22, this increase was only significant in uteri (+ 50 % ; $p < 0.01$) ; between days 22 and 23, it was + 204 % ($p < 0.01$) in the uterus and + 591 % ($p < 0.001$) in the peripheral plasma.

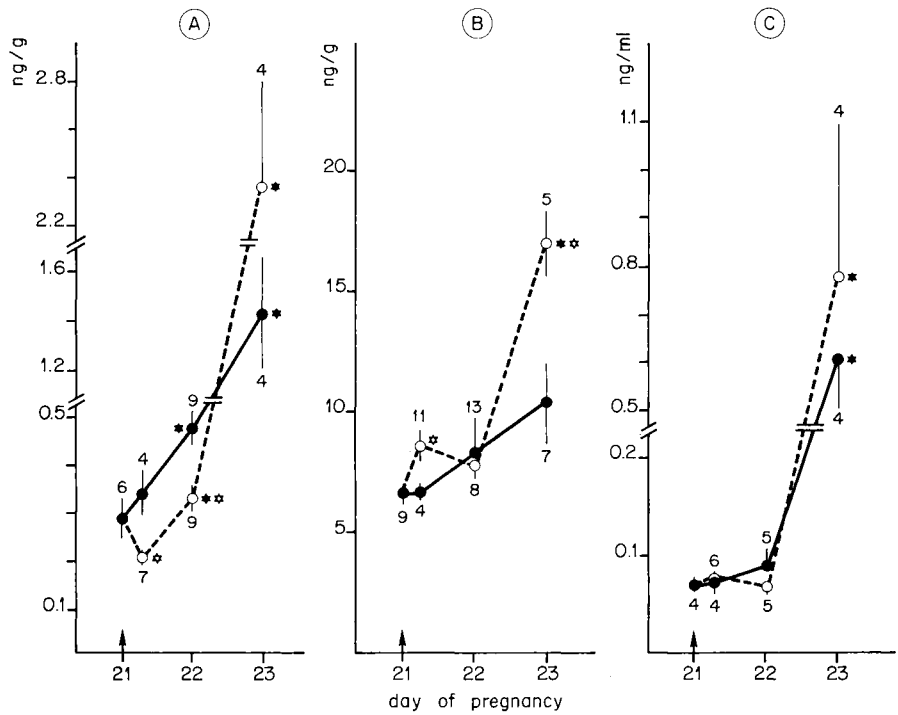

FIG. 4. — *Estradiol* (E_2) *concentrations in control* (•——•) *and isotonic* NaCl-*treated* (o---o) *rats.* See legend of figure 2.

A : uterus, B : ovaries, C : peripheral plasma.

Six hours after i.u. isotonic saline injection, uterine concentrations of E_2 were significantly lower (− 30 % ; $p < 0.05$), although at this stage ovarian concentrations increased (+ 30 % ; $p < 0.05$) and plasma levels were not different. Thus, the ut:pl ratio decreased (− 34 % ; $p < 0.05$) within the next 6 h after treatment. Twenty-four hours later, *i.e.* at 10 a.m. on day 22, the levels of E_2 were always low in the uterine tissues of treated rats (− 30 % ; $p < 0.01$). At 10 a.m. on day 23, *i.e.* 48 h after treatment, the uterine levels of E_2 were within the range of the controls. Since plasma levels of E_2 were also similar in treated and untreated rats, the ut:pl ratio was not different in either group of animals at term.

As shown in figure 5, the concentrations of E_1 in uteri or ovaries of treated animals remained within the range of control preparturient rats. Moreover, on days 22 and 23 of pregnancy, the levels of E_2 and E_1 in uterine venous blood were always similar to the values of peripheral plasma (table 2). In animals from which uterine tissues and peripheral plasma had been simultaneously sampled, we noted a highly positive correlation ($n = 20$, $r = 0.822$; $p < 0.001$) among E_2 levels in both compartments.

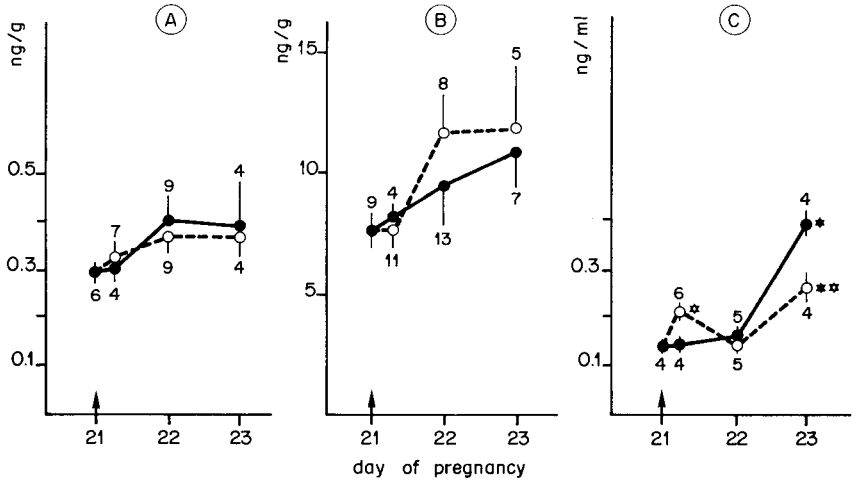

FIG. 5. — *Estrone* (E_1) *concentrations in control* (•——•) *and isotonic* NaCl-*treated* (o---o) *rats.* See legend of figure 2.

A : uterus, B : ovaries, C : peripheral plasma.

TABLE 2

Estradiol (E_2) and estrone (E_1) concentrations in uterine venous plasma of control and saline-treated rats (means ± SEM)

Day of pregnancy	E_2 (pg/ml)		E_1 (pg/ml)	
	Control rats	Treated rats	Control rats	Treated rats
21	82 ± 5 (4)	80 ± 9 (7)	179 ± 15 (5)	220 ± 17 (7)
22	80 ± 10 (6)	62 ± 5 (4)	161 ± 30 (6)	152 ± 21 (4)
23	602 ± 216★ (4)	882 ± 279★ (5)	352 ± 74 (4)	246 ± 42 (5)

The number of animals is shown in parentheses.
★ : significantly different from values at previous stage of pregnancy.

Discussion.

When performed on day 21 of pregnancy, injection of isotonic saline into the uterus of pregnant rat or only handling the uterus seriously impaired parturition ; when the rats were treated earlier or later in pregnancy, there was

little or no impairment. The impairment could be due to a failure in uterine contractility related to a change in the epinephrine-norepinephrine balance in the uterus (Maltier and Cavaillé, 1975). Therefore, the present findings clearly show that other hormonal discrepancies related to plasma and tissue steroid levels might also be implicated in saline-induced impairment of parturition. After both treatments, a transient increase in the uterine concentration of P was noted. This would reflect a rise in plasma P originating from the adrenals (surgical stress : Yoshinaga *et al.*, 1967 ; Fajer *et al.*, 1971) or from increased secretion of ovarian P (Pepe and Rothchild, 1973) since Legrand *et al.* (1979) showed that uterine P concentrations mostly depend on changes in circulating P levels. The transient increase of P and 20α-HP in the ovaries suggests that the synthesis of both progestins was stimulated. Careful analysis of the changes in ovarian 20α-OHSDH or Δ_5-3β-OHSDH activities in both control and saline-treated rats did not show any clear correlation between the concentrations of progestin in ovaries and enzymatic activity. This was also pointed out by Lacy *et al.* (1976) who consider that the biochemical method validated *in vitro* by Wilcox and Wiest (1966) and Kuhn and Briley (1970) does not « accurately reflect the *in vivo* activity of the enzyme » since other factors such as substrate or cofactor availability may regulate hormonal synthesis *in vivo.* Moreover, we have no rational explanation for the concomitant increase of P and 20α-HP in the ovary of saline-treated rat, unless puncture or handling the uterus, a severe aggression on the fetus (Legrand and Maltier, 1981a), could induce the release of a feto-placental luteotrophic substance, shown to stimulate the luteal function of mid-pregnant rat and induce a characteristic parallel rise in both gestagens (Sin *et al.*, 1971). A change in the endometrial secretory PGE/$PGF_{2\alpha}$ ratio, however, cannot be excluded.

The elevation of the uterine P level was transient ; within 24-48 h after both treatments, uterine P concentrations decreased to within a normal or subnormal range. Therefore, it cannot be considered that a « progesterone block » (Csapo, 1969) at term accounts for abnormal delivery.

In spite of a highly positive correlation among circulating E_2 levels and E_2 concentrations in the uteri, the decline in E_2 observed in uterine tissues 6 h after i.u. isotonic saline injection does not result from a clearance of E_2 in peripheral plasma. The diminution of the uterine concentrations of E_2 may be a local effect of the transient increase in P levels. This concept agrees with previous evidence reported in rats (Resko *et al.*, 1976) and rabbits (Batra *et al.*, 1978), demonstrating that progesterone administration suppresses the accumulation of E_2 by uterine tissues, presumably by reducing the levels of E_2 receptors. According to the work of Wahawisan and Gorell (1980), this effect could also result from an inhibition of uterine 17β-OHSDH that interconverts E_2 and E_1 in the rat uterus, favoring E_2 production. In our experiments, such an hypothesis seems unwarranted since uterine levels of E_1 were unchanged. Later, within 24-48 h after i.u. isotonic saline injection, changes in uterine concentrations of E_2 reflected those in peripheral plasma. Moreover, our results, demonstrating the similarity of E_1 and E_2 levels in uterine venous blood and peripheral plasma, indicate that estrogens do not originate from the placentae ; this is in agreement

with previous data obtained *in vitro* by Sybulski (1970) and Townsend and Ryan (1970).

As shown by the present work, the most important changes in response to surgical treatment were seen in uterine concentrations of both progestins and estrogens within 6-24 h. When complete or partial parturition was delayed, this delay varied between 6 and 24 h. Thus, when the chronology of the normal sequence of changes in P and E_2 occurring on day 21 was delayed, we noted a similar delay in the timing of delivery.

When treatment was applied earlier on day 20, the uterine P/E_2 ratio returned to normal on day 21 and, consequently, all the deliveries were complete. Our experimental data demonstrate that an adequate level of uterine E_2 is of major importance at this stage of pregnancy. Thus, a single injection of E_2-dipropionate, presumed to enhance plasma and uterine levels of E_2, resulted in 88 % of complete delivery when given on day 21 simultaneously with i.u. isotonic saline injection. Moreover, in these conditions we never observed suppressed parturition. All these observations confirm the hypothesis of Catala and Deis (1973) and Dukes *et al.* (1974) that day 21 is a critical period in the onset of parturition in rats. We suggest that this stage of pregnancy is the time when the sequence of hormonal events leading to normal parturient activity in the rat uterus is organized.

The transient changes in uterine concentrations of both P and E_2 noted immediately after i.u. isotonic saline or handling of the uterus were also followed by a modification in the uterine balance between epinephrine and norepinephrine (Maltier and Cavaillé, 1975). Thus, the chronology of these hormonal events suggests that the changes in catecholamine concentrations in the preparturient uterus of rat could be a consequence of changes in the P and/or E_2 levels. This is in agreement with previous data which show that steroid hormones may regulate the uterine levels of catecholamines in the pregnant rat at term (Maltier and Cavaillé, 1978 ; Maltier *et al.*, 1980).

Thus, subsequent changes in the adrenergic reactivity of the uterus may account for the partially delayed or suppressed delivery noted in our experimental rats and could explain the impairment of the electrical activity found in the myometrium of saline-treated rats (Legrand and Maltier, 1981 b).

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Résumé. *Existence d'une période critique dans la sensibilité utérine à l'œstradiol et à la progestérone au moment de la parturition chez la Ratte.*

Chez la ratte, une injection intra-utérine de 0,5 ml de chlorure de sodium isotonique ou la manipulation de l'utérus pratiquée au 21e jour, 10 h de la gestation provoque 70 % à

98 % de parturitions anormales. Les deux traitements sont immédiatement suivis d'une augmentation transitoire des concentrations de progestérone dans l'ovaire (+ 52 %, $P < 0,05$) et l'utérus (+ 74 %, $P < 0,05$). Il en est de même pour les concentrations de 20α-dihydroprogestérone dans l'ovaire (+ 89 %, $P < 0,001$) et l'utérus (+ 470 %, $P < 0,01$). A l'inverse, sous l'effet du traitement, les concentrations utérines de l'œstradiol diminuent brutalement (− 30 %, $P < 0,05$) malgré une élévation transitoire du niveau ovarien de l'hormone (+ 30 %, $P < 0,05$). Au 22^e jour, 12 h de gestation, les concentrations utérines de l'œstradiol restent plus faibles que celles notées chez les rattes contrôles (− 30 %, $P < 0,01$). La signification physiologique de ces changements hormonaux et leurs conséquences sur la réactivité de l'utérus préparturient sont discutées. En outre, nos résultats démontrent que le 21^e jour de la gestation chez la ratte est la période critique pour l'initiation de la parturition puisque les mêmes traitements appliqués avant ou après cette date n'entraînent que peu ou pas de perturbations.

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