- plasma myo-inositol levels in uremia and experimental neuropathy. *Lancet*, *i*: 1137 (1973).
5. Eagle, H., Oyama, V. I., Levy, M., and Freeman, A. E.: Myo-inositol as an essential growth factor for normal and malignant human cells in tissue culture. *J. Biol. Chem.*, **226**: 191 (1957).
 6. Edelmann, C. M., Jr., and Spitzer, A.: The maturing kidney, a modern view of well-balanced infants with imbalanced nephrons. *J. Pediatr.*, **75**: 509 (1969).
 7. Hanks, L. V., Politzer, W. M., Touster, O., and Anderson, L.: Myo-inositol catabolism in human pentosurics. *Ann. N. Y. Acad. Sci.*, **165**: 564 (1969).
 8. Howard, C. F., Jr., and Anderson, L.: Metabolism of myo-inositol in animals. II. Complete catabolism of myo-inositol-¹⁴C by rat kidney slices. *Arch. Biochem. Biophys.*, **118**: 332 (1967).
 9. Lewin, L. M., Szeinberg, A., and Lepkifker, E.: Gas chromatographic measurement of myo-inositol in human blood, cerebrospinal fluid and seminal fluid. *Clin. Chim. Acta*, **45**: 361 (1973).
 10. Melmed, S., Bank, H., and Lewin, L. M.: Clinical significance of increased serum myo-inositol levels. *Isr. J. Med. Sci.*, **10**: 1518 (1974).
 11. Melmed, S., Lewin, L. M., and Bank, H.: Myo-inositol clearance in renal failure and in patients with normal kidney function. *Amer. J. Med. Sci.*, **274**: 55 (1977).
 12. McKibbin, J. M.: The determination of inositol, ethonolamine and serine in lipids. *Methods Biochem. Anal.*, **7**: 111 (1959).
 13. Ogasa, K., Kuboyama, M., Kiyosawa, I., Suzuki, T., and Itoh, M.: The content of free and bound inositol in human and cow's milk. *J. Nutr. Sci. Vitaminol.*, **21**: 129 (1975).
 14. Passwell, J. H., Modan, M., Brish, M., Orda, S., and Boichis, H.: Fractional excretion of uric acid in infancy and childhood. *Arch. Dis. Childhood*, **49**: 878 (1974).
 15. Perles, R., and Colas, M. C.: Determination microbiologique du méso inositol sanguin. *Clin. Chim. Acta*, **5**: 95 (1960).
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Cord blood	newborns
17 α -hydroxyprogesterone	ovarian maturation
infancy	total corticosteroids

Ontogenic Study of Plasma 17 α -Hydroxyprogesterone in the Human. I. Postnatal Period: Evidence for a Transient Ovarian Activity in Infancy

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Summary

Plasma concentrations of 17 α -hydroxyprogesterone (OHP) were measured by a specific and sensitive radioimmunoassay in 348 blood specimens of male and female infants from birth to 2 years of age. Total corticoids levels were assayed by a competitive protein binding technique.

OHP levels were higher in the cord than in the peripheral blood of both the mother and the newborn. At term OHP cord levels were higher in female than in male infants. Mean peripheral concentrations of OHP were 419 ± 217 in boys and 431 ± 175 ng/dl in girls in the first day of life and decreased during the first week of life to 70 ± 37.5 and 95 ± 39 ng/dl in male and female infants, respectively. Thereafter, a sex-linked difference in the pattern of OHP plasma concentrations was observed during infancy and, moreover, this dimorphism varied with age, values being higher in boys at 1-2 months but higher in girls at 6-9 months of age. Total corticoids values did not vary significantly with either sex or age.

The pattern of OHP in boys closely parallels that which we described previously for testosterone and further documents the postnatal endocrine activity of the testis. The pattern of OHP in girls suggests that in human infant the ovaries exhibit a moderate and rhythmic endocrine activity which lasts at least until the end of the first year of life.

Speculation

It has been shown that in human infant the testis has a marked and transient (for about 4 months) endocrine secretion (OHP and testosterone) after the postnatal activation of the hypothalamopituitary function. In contrast, in female infants, the ovaries exhibit a moderate, rhythmic, but more prolonged endocrine secretory activity (OHP and estradiol). This could result from a pulsatile secretion with great amplitudes but a low tonic gonadotrophin activity in infancy. It is speculated that in the ovary a more sustained luteinizing hormone (LH) (or LH + follicle-stimulating hormone (FSH)) stimulation could be necessary to achieve full maturation of its steroidogenic enzymes, in particular, of the aromatase.

We have been able to demonstrate in previous studies (9-11, 13) that there is transient postnatal testicular activity in the human. This phenomenon appears to be under the control of the hypothalamic-hypophyseal axis since circulating levels of LH and FSH are markedly elevated in this period (6, 13, 37). A similar postnatal activation of the hypothalamic-hypophyseal system was also observed in female infants (6, 13, 37). The purpose of this work was to investigate whether the infantile ovary was capable of responding to the elevated FSH and LH

levels which are seen in this period. The study of the pattern of 17 α -hydroxyprogesterone (41) plasma levels has been chosen as an indicator of gonadal activity because of the relatively large volume of plasma required to measure accurately estrogens levels and because of ethical limitation in the quantity of blood obtainable from small babies.

MATERIALS AND METHODS

SUBJECTS

Mixed venous and arterial blood samples were obtained immediately after cord clamping in 23 male and 22 female infants, the product of uneventful pregnancies and spontaneous vaginal deliveries. The duration of gestation varied from 32–41 weeks. Group I comprised full term babies (38–41 weeks, 17 males and 15 females) whereas group II consisted of preterm babies (32–37 weeks, six males, six females). Peripheral antecubital venous blood was also obtained from three mothers of full term babies at the time of cord clamping.

Blood obtained by heelprick or superficial venous puncture was directly drawn into tubes containing lyophilized heparin from 303 healthy full-term infants aged 1 day to 2 years. Informed consent was obtained from parents and their physicians. At different times within the first day of life 15 male and 16 female infants were studied. These subjects were the same as those in whom we previously reported plasma levels of testosterone and androstenedione (9). Between 1 and 60 days of age the study comprised 63 male and 43 female infants; the group of infants aged 2–12 months consisted of 78 males and 50 females whereas that of infants aged 1–2 years encompassed 17 boys and 19 girls. Plasmas were immediately decanted and stored at -20° until analyzed.

STEROID DETERMINATION

Plasma concentrations of OHP were measured by a sensitive and specific radioimmunoassay (RIA) technique detailed elsewhere (7). In brief, 0.1–2 ml of plasma were extracted with ethyl ether after the addition of [3 H]OHP (spec act = 44.8 Ci/mM – NEN) or [3 H]testosterone (spec act = 91 Ci/mM – NEN) for recovery purpose. Water blanks and standards were run in all assays. The dried extracts were chromatographed on microcolumns of celite using ethylene glycol as stationary phase (10). The antiserum used in the present study was raised in rabbit immunized with the mono-3-(*O*-carboxymethyl)-oxime bovine serum albumin derivative of OHP. This antiserum was highly specific (12), as it cross-reacted only with 17 α -hydroxy-pregnenolone (10%) and 3 α ,17 α -dihydroxy-5 β -pregnan-20-one (15%) among the 40 steroids tested. Antiserum had a K_a of 3.2×10^{10} liters/M $^{-1}$ and was used at final dilution of 60,000. The limit of sensitivity was 5–10 pg, i.e. <1 ng/dl. In all the samples assayed detectable amounts of OHP were above the limit sensitivity of the method. The final recovery of the RIA was $76.6 \pm 5.2\%$ and the coefficient of interassay variation was 10%. Standard curves relating logit/log coordinates of the percent binding and steroid were computerized using a PDP-8 Digital Equipment computer. In most of the samples using a competitive binding technique (21) plasma levels of cortisol were also measured.

STATISTICAL ANALYSIS

Differences between the different groups of subjects were analyzed, unless specified, by the Student *t*-test. The Wilcoxon two-sample rank test was also used. Median and mean values were calculated in all groups and analyzed; they did not differ significantly either in their absolute values or in the significance of differences observed between various groups. In this report results are given, unless notified, as mean and standard deviation for each age and sex group.

RESULTS

PLASMA CONCENTRATIONS OF OHP IN CORD BLOOD

Large variations in the individual plasma concentrations of OHP were observed in the total group and are illustrated in Figure 1. The subjects were analyzed according to sex and prematurity and results obtained in all subgroups are given in Table 1. When comparison was made between male versus female preterm babies or between the total group (male and female) of preterm versus full term newborns, no difference was observed. However, mean levels of OHP in the group of full-term babies were significantly (Wilcoxon test $2\alpha < 0.01$) higher in the female than in the male. Finally, when the analysis considered male and female separately in relation to the time of pregnancy OHP levels were significantly ($2\alpha < 0.01$) higher in full-term girls and significantly ($2\alpha < 0.01$) lower in full-term boys than in the preterm infants of the corresponding sex.

ANDROGENS AND OHP LEVELS IN PERIPHERAL BLOOD OF MOTHERS AT TIME OF DELIVERY

Mean (± 1 SD) levels, expressed in ng/dl, found in the peripheral blood of mothers at the time of delivery, were 102.6

Fig. 1. Individual values of OHP in mixed venous cord blood of 41 newborns in relation to duration of fetal life.

Table 1. Plasma concentrations (nanograms per dl) of 17 α -hydroxyprogesterone in cord blood of full-term and preterm newborns

Infants	Total group	Male	Female	P ¹ (male vs. female)
Full-term				
n	32	17	15	
Median	2108	1752	2341	
Mean	2427	1865	3064	
SD	± 1314	± 1014	± 1352	<0.01
Range	(834–5483)	(834–5215)	(1363–5483)	
Preterm				
n	12	6	6	
Median	2386	2867	2288	
Mean	2744	3055	2433	NS
SD	± 1657	± 1962	± 818	
Range	(919–6244)	(1072–6244)	(919–5047)	
P ¹ (full-term vs. preterm)	NS	<0.01	<0.01	

¹ Analysis made with Wilcoxon test.

± 43.2 for testosterone, 239.3 ± 84.1 for Δ^4 -androstenedione, and 782.7 ± 227.5 for OHP. The latter hormone was significantly ($P < 0.001$) lower in the mother than in the cord.

OHP LEVELS IN PERIPHERAL BLOOD OF NEWBORNS DURING FIRST DAY OF LIFE

Individual values in relation to the hours of postnatal life and sex are given in Figure 2. They were very high in comparison with the levels found in normal adult men (118 ± 34 ng/dl) or women (follicular phase (FP) = 46 ± 16 , luteal phase (LP) = 241 ± 71 ng/dl). Blood concentration of OHP decreased rapidly within the first 24 hr of life and its correlation with time was highly significant ($P < 0.001$) and not different according to sex ($r = 0.58$ and 0.69 in male and female, respectively). The mean ± 1 SD values of OHP during the first day of life were also not different between boys (419 ± 216.5 , range 153–886, median = 433 ng/dl) and girls (431 ± 174.5 ; range 200–844, median = 435 ng/dl). Mean levels of OHP were however, considerably lower ($P < 0.001$) in peripheral blood than in cord blood, contrary to what we previously described in the same infants for testosterone, for Δ^4 -androstenedione (9) (as summarized in Fig. 3), and also for dehydroepiandrosterone (DHA) (23).

The circulating levels of these four hormones were particularly high at birth; all showed a rapid decline during the first day of life. However, the significant correlation between hormone levels and hours of postnatal life that we found for OHP was loose and not statistically significant for the three androgens, testosterone, Δ^4 -androstenedione, and dehydroepiandrosterone.

OHP LEVELS DURING FIRST 2 MONTHS OF LIFE

Individual mean ± 1 SD of OHP levels found in girls and boys are given in Figure 4 and Table 2. Blood concentrations of OHP further decreased during the first week of life to mean values of 80 ± 46 ng/dl in male and 95 ± 39 ng/dl in female neonates. Thereafter, the pattern was different according to sex. In female babies OHP levels plateaued at mean levels of 100–150 ng/dl throughout this period. In male infants a secondary increase in OHP levels was observed to reach maximal values between 30 and 60 days of age (Fig. 4, Table 2). In this age group the difference according to sex was significant ($P < 0.001$).

Individual plasma concentrations of OHP observed in this period in boys and girls are given in Figures 5 and 6, respectively. Again the pattern was different between sexes. In male infants OHP levels decreased progressively from 2–7 months of age, at which time values remained at similar levels until 2

Fig. 2. Concentration of OHP in peripheral venous blood of full-term infants in relation to the hours of postnatal life.

Fig. 3. Comparison between the mean concentrations of testosterone (T), Δ^4 -androstenedione (Δ^4), and OHP obtained in cord blood as compared to those found in peripheral blood on the first day of life in normal male and female newborns. Median values ($\diamond$) are also reported. (Values for T and Δ^4 , summarized from Reference 10, are given in nanograms per dl, whereas those of OHP are in nanograms per ml.)

Fig. 4. Individual and mean (± 1 SD) plasma concentrations of OHP during the first 60 days of life, in male (left) and female (right) newborn infants.

Table 2. Mean levels (nanograms per dl) of 17 α -hydroxyprogesterone in male and female infants in relation to age

Age	Male		Female	
	n	Mean $\pm$ 1 SD	n	Mean $\pm$ 1 SD
Days				
>1-2	3	282 $\pm$ 100	2	211 $\pm$ 10
2-3	6	96 $\pm$ 53	3	104 $\pm$ 55
3-7	18	80 $\pm$ 46	6	95 $\pm$ 39
7-11	7	123 $\pm$ 40	8	148 $\pm$ 45
12-30	11	150 $\pm$ 68	13	128 $\pm$ 54
30-60 ¹	20	201 $\pm$ 79	11	103 $\pm$ 49
Months				
2-3	14	111 $\pm$ 57	10	97 $\pm$ 57
3-4	13	74 $\pm$ 41	7	75 $\pm$ 43
4-5	12	56 $\pm$ 37	6	62 $\pm$ 24
5-7	11	50 $\pm$ 21	9	46 $\pm$ 24
7-9 ²	17	29 $\pm$ 21	10	60 $\pm$ 42
9-12	11	28 $\pm$ 21	8	43 $\pm$ 25
12-24	17	24 $\pm$ 13	19	27 $\pm$ 11

¹ Values higher in male than in female ($P < 0.001$).

² Values higher in female than in male ($P < 0.01$).

years of age (Table 2). In female infants OHP levels decreased more slowly with a range in values larger than in boys. Between 3 and 12 months of age mean values remained higher in female than in male infants of the same age and also higher than in girls aged 1-2 years, a period during which OHP levels are similar in both sexes. However, when results were analyzed for infants grouped by intervals of 2 months of age, OHP was only significantly ($P < 0.01$) higher in girls than in boys in the group 7-9 months of age.

TOTAL CORTICOID LEVELS IN INFANCY

The competitive protein binding method used to estimate cortisol is not fully specific and does not differentiate possible variations with age, particularly in the first month of life, in the ratio of cortisone to cortisol. This measurement was made only to eliminate the possible interference of acute or nonclinically evidenced chronic stress. Total corticoid levels were not different either with age or with sex during the first 2 years of life. Mean values were 9.5 ± 4.3 μ g/dl in male infants and 9.03 ± 5.6 μ g/dl in female infants.

DISCUSSION

Mean levels of OHP in the mother at the time of delivery are comparable to those of the third trimester of pregnancy reported in the literature (14, 33, 39, 40); we are not aware of any study of the simultaneous measurement of OHP at the time of delivery in the peripheral blood of the mother, cord blood, and peripheral blood of the newborn. Our results, showing in the same subjects a higher concentration of OHP (but not of Δ^4 -androstenedione) in the cord than in both sides of the placental barrier (mother and fetus) suggest an important placental production of OHP. This view is also supported by the fact that OHP decreases significantly with time within the first 24 hr of life and by the fact that this fall is more rapid than that of Δ^4 -androstenedione (9) or that of DHA (23), steroids of predominantly adrenal fetal origin.

Observed values of plasma OHP concentration in the cord are in good agreement with those previously reported (38, 39). However, in these two previous studies, the duration of pregnancy was not detailed and no sex difference was described. Although the range of values for both sexes is extremely large, it would appear from the present study that OHP levels have a tendency to decrease in the male and to increase in the female towards term. Furthermore, OHP levels are significantly lower

in the cord blood of male babies at term. However, as no sex difference in OHP levels were observed in the cord blood, this discrepancy requires further study.

Values for plasma OHP in normal newborns after 1 day of age are scarce in the literature (3, 32, 39) and are in the same range as those we observed. However, in these reports, infants 1-2 months or 1-12 months old were considered as a homogeneous group. The changes in plasma OHP concentrations during the first year of life shown here confirm our earlier report (8). A pattern of OHP in infancy appeared recently in the literature (38). In the study of Winter *et al.* (38) the pattern described seems to agree with the present report. However, the authors do not give any individual or group values and do not mention any sex difference in OHP levels after 4 months of age.

From our data there is a sexual dimorphism in the pattern of OHP plasma concentration during infancy and, moreover, this OHP dimorphism varies with age; values are higher in boys at 1-3 months of age but higher in girls at 7-9 months.

After a significant rise observed between the first and the third week of life, OHP levels are higher at 1-3 months of age in male infants, and decline thereafter. Although the variation in plasma concentration of OHP are only 2-fold in amplitude, its pattern is very similar to that which we reported for testosterone and Δ^4 -androstenedione (9, 11, 13) and which is summarized in Figure 7. The contribution of the testicular secretion to the peripheral pool of OHP is well documented in the adult male (30, 36). In the young infant the sex difference in OHP further evidences the postnatal endocrine activity of the testis.

Is OHP a good indicator of ovarian activity? In our previous studies of the pattern of steroid hormones of primarily adrenal origin, Δ^4 -androstenedione (13) or dehydroepiandrosterone (23), no sex difference was observed after 6 months of age. In this report cortisol levels were not different according to sex throughout infancy. The higher levels of OHP in girls after 6 months of age suggest an ovarian endocrine activity. In adult-

Fig. 5. Individual and mean (± 1 SD) plasma concentrations of OHP in normal male infants from 1-24 months of age.

Fig. 6. Individual and mean (± 1 SD) of plasma concentrations of OHP in normal female infants, 1-24 months old.

Fig. 7. Profile of the evolution of the concentrations in testosterone (Testo), Δ^4 -androstenedione (Δ^4), and OHP during the first year of life in normal infants. These patterns were drawn from the mean values obtained at successive ages. (Data are summarized from the present study, from References 7-10, and from unpublished observations.)

hood the cyclic activity of the ovary is reflected by the cyclic secretion of sexual steroids, mainly 17β -estradiol, OHP, and progesterone. Although the primordial origin of OHP in the ovary itself is still debated and might represent an index of either follicular (5, 31) or luteal maturation (20, 22), or reflect the LH, FSH surges (1, 2), its ovarian production is not questioned.

The original study of Bidlingmaier *et al.* (4) showed that the female infant is capable, at least in some cases, of important surges of estradiol, as throughout the first year of life. They observed pubertal levels of estradiol in some but not all female infants.

In another study, estradiol levels were, in both sexes, significantly higher than in prepubertal children during the first 4 months of life only (38). These age differences in estradiol pattern resemble that described for gonadotrophins in infancy: high levels throughout the first year of life in one study (13), significantly higher levels only in the first 4 months of life in the other (37). However, in both reports, a considerable variability in LH/FSH levels was observed, suggesting a wide pulsatility in gonadotropin secretion in infancy.

If one admits that OHP is an index of follicular maturation, one could be surprised of the apparent unresponsiveness of the ovary at the time of high LH/FSH postnatal secretion (13, 37), a time when the testes have an important steroidogenic activity (production of testosterone, OHP).

In contrast with earlier studies (35), more recent histologic reports show that 1) the ovary is never quiescent after birth; 2) ovaries at all ages (from 2-22 months and 2-11 years) show follicular growth (24), Graafian follicles (29), ripening of oocytes, definite growth, and atresia continuously in infancy and childhood (19, 26, 27, 34), and 3) that infantile follicles stain for glycogen and alkaline phosphatase in a manner similar to those from postpubertal ovaries (25). This follicular maturation seems to be more important at 2-4 (24) or 1-4 months of age

(26). Even in infancy these follicles present all the elements so well recognized in the adult ovary, including partial luteinization of the theca interna which indicates the influence of gonadotrophins.

From experimental studies it has been shown that in rat the capacity of the ovarian adenylate cyclase and estradiol secretion to respond to LH are both acquired during the second week of postnatal life (16, 17, 28). In the immature rat ovary the aromatizing system is practically inactive (15), although the enzymes necessary for the synthesis of progesterone and androgens are very active and can be stimulated immediately by the gonadotrophins. However, after a constant stimulation by LH, but not after multiple injections, the immature ovary is capable of increasing its estradiol secretion. On the other hand, by 2 months of age the rhesus monkey ovary can convert androstenedione to estradiol *in vitro* at rates similar to those of the adult ovary (18).

From these and our own data, it can be suggested that in the human infant the ovaries exhibit a moderate and rhythmic endocrine activity (OHP, estradiol) which lasts at least until the first year of life. This activity is related to the marked pulsatile secretion of gonadotrophins seen at this age. The aromatizing system would need a more sustained LH stimulation (increase in tonic secretion) to reach full maturation. This occurs in pubertal development and is one of the mechanisms responsible for the changes in ovarian secretion seen at this time.

REFERENCES AND NOTES

1. Abraham, G. E., Odell, W. D., Swerdloff, R. S., and Hopper, K.: Simultaneous radioimmunoassay of plasma FSH, LH, progesterone, 17α -hydroxyprogesterone and estradiol-17 beta during the menstrual cycle. *J. Clin. Endocrinol. Metab.*, **34**: 312 (1972).
2. Aedo, A. R., Landgren, B. M., Cekan, Z., and Diczfalussy, E.: Studies on the pattern of circulating steroids in the normal menstrual cycle. 2. Levels of 20α -dihydroprogesterone, 17α -hydroxyprogesterone and 17α -hydroxypregnenolone and the assessment of their value for ovulation prediction. *Acta Endocrinol.*, **82**: 600 (1976).
3. Atherden, S. M., Edmunds, A. T., and Grant, D. B.: Plasma 17α -hydroxyprogesterone in newborn infants with congenital adrenal hyperplasia and in infants with normal adrenal function. *Arch. Dis. Childhood*, **49**: 192 (1974).
4. Bidlingmaier, F., Versmold, H., and Knorr, D.: Plasma estrogens in newborns and infants. In: M. G. Forest and J. Bertrand: *Endocrinologie Sexuelle de la période Périnatale*, Vol. 32, pp. 299-314 (Editions INSERM, Paris, 1974).
5. Channing, C. P.: Steroidogenesis and morphology of human ovarian cell types in tissue culture. *J. Endocrinol.*, **45**: 2017 (1969).
6. Faïman, C., and Winter, J. S. D.: Sex difference in gonadotropin concentrations in infancy. *Nature*, **232**: 130 (1971).
7. Forest, M. G.: Use of highly specific antibodies against 17α -OH-progesterone in a simplified non chromatographic RIA and in the simultaneous determination of sex hormones in human plasma. *Hormone Res.*, **7**: 260 (1976).
8. Forest, M. G., and Bertrand, J.: Ontogeny of gonadal steroids in human: Perinatal period. Proceedings of the VIIth Meeting of International Study Group of Steroid Hormones, Rome, December 3-5, 1975 (In press).
9. Forest, M. G., and Cathiard, A. M.: Pattern of plasma testosterone and Δ^4 -androstenedione in normal newborns: Evidence for testicular activity at birth. *J. Clin. Endocrinol. Metab.*, **41**: 977 (1975).
10. Forest, M. G., Cathiard, A. M., and Bertrand, J.: Total and unbound testosterone levels in the newborn and in normal and hypogonadal children: Use of a sensitive radioimmunoassay for testosterone. *J. Clin. Endocrinol. Metab.*, **36**: 1132 (1973).
11. Forest, M. G., Cathiard, A. M., and Bertrand, J.: Evidence of testicular activity in early infancy. *J. Clin. Endocrinol. Metab.*, **37**: 148 (1973).
12. Forest, M. G., Mappus, E., and Cuilleron, C. Y.: *O*-(carboxymethyl)oxime steroidal haptens linked in the C_3 position: Study of the characteristics of antibodies against 17α -hydroxyprogesterone and testosterone and of their evolution with time. *Steroids*, **28**: 815 (1976).
13. Forest, M. G., Sizonenko, P. C., Cathiard, A. M., and Bertrand, J.: Hypophysogonadal function in human during the first year of life. I. Evidence for testicular activity in early infancy. *J. Clin. Invest.*, **53**: 819 (1974).
14. Holmdahl, T. H., and Johanson, E. D. B.: Peripheral plasma levels of 17α -hydroxyprogesterone during human pregnancy. *Acta Endocrinol. (Kbh)*, **71**: 765 (1972).
15. Kareim, A., and Samuels, L. T.: The influence of FSH and FSH + LH on steroidogenic enzymes in the immature mouse ovary. *Endocrinology*, **95**: 660 (1974).
16. Lamprecht, S. A., Zor, U., Tsafiriri, A., and Lindner, H. R.: Action of prostaglandin E_2 and of luteinizing hormone on ovarian adenylate cyclase, protein kinase and ornithine decarboxylase activity during postnatal development and maturity in the rat. *J. Endocrinol.*, **57**: 217 (1973).

17. Lamprecht, S. A., Cohen, F., Ausher, J., and Zor, U.: Hormonal stimulation of oestradiol-17 β release from rat ovary during early postnatal development. Fifth International Congress of Endocrinology, Hamburg, July 18-24, 1976, p. 363. (Abstract 881).
18. Lemons, J. A., Foster, D. L., and Jaffe, R. B.: Aromatization by the immature rhesus monkey ovary. *Endocrinology*, **94**: 1181 (1974).
19. Lintern-Moore, S., Peters, H., Moore, G. P. M., and Faber, M.: Follicular development in the infant human ovary. *J. Reprod. Fertil.*, **39**: 53 (1974).
20. Lloyd, C. W., Lobotsky, J., Baird, D. T., McCracken, J. A., Weisz, J., Pupkin, M., Zanartu, J., and Puga, J.: Concentration of unconjugated estrogens, androgens and gestagens in ovarian and peripheral venous plasma of women: the normal menstrual cycle. *J. Clin. Endocrinol. Metab.*, **32**: 155 (1971).
21. Loras, B., Roux, H., and Philippe, M. H.: Dosage du cortisol plasmatique et urinaire par liaison compétitive aux protéines. *Ann. Endocrinol. (Kbh)*, **31**: 383 (1970).
22. Mikhail, G., Zander, J., and Allen, W. H.: Steroids in human ovarian vein blood. *J. Clin. Endocrinol. Metab.*, **23**: 1267 (1963).
23. de Peretti, E., and Forest, M. G.: Unconjugated dehydroepiandrosterone plasma levels in normal subjects from birth to adolescence in human: The use of a sensitive radioimmunoassay. *J. Clin. Endocrinol. Metab.*, **43**: 982 (1976).
24. Peters, H., Himelstein-Braw, R., and Faber, M.: The normal development of the ovary in childhood. *Acta Endocrinol. (Kbh)*, **82**: 617 (1976).
25. Pinkerton, J. H. M., McKay, D. G., Adams, E. C., and Herting, A. T.: Development of the human ovary: a study using histochemical technics. *Obstet. Gynecol.*, **18**: 152 (1961).
26. Polhemus, D. W.: Ovarian maturation and cyst formation in children. *Pediatrics*, **11**: 588 (1953).
27. Pryse-Davies, J., and Dewhurst, C. J.: The development of the ovary and uterus in the foetus, newborn and infant: A morphological and enzyme histochemical study. *J. Pathol.*, **103**: 5 (1971).
28. Sashida, T., and Johnson, D. C.: The response of the immature rat ovary to gonadotrophins: Acute changes in cyclic AMP, progesterone, testosterone, androstenedione, and oestradiol after treatment with PNS or FSH + LH. *Acta Endocrinol. (Kbh)*, **82**: 413 (1976).
29. Sauramo, H.: Histology and function of the ovary from the embryonic period to the fertile age. *Obstet. Gynecol. Scand.*, **333** (Suppl. 2): 2 (1954).
30. Strott, C. A., Yoshimi, T., and Lipsett, M. B.: Plasma progesterone and 17-hydroxyprogesterone in normal men and children with congenital adrenal hyperplasia. *J. Clin. Invest.*, **48**: 930 (1969).
31. Strott, C. A., Yoshimi, T., Ross, G. T., and Lipsett, M. B.: Ovarian physiology: Relationship between plasma LH and steroidogenesis by the follicle and corpus luteum: Effect of hCG. *J. Clin. Endocrinol. Metab.*, **29**: 1157 (1969).
32. Tea, N. T., Castanier, M., Roger, M., and Scholler, R.: Simultaneous radioimmunoassay of plasma progesterone and 17-hydroxyprogesterone: Normal values in children, in men and in women throughout the menstrual cycle and in early pregnancy. *J. Steroid Biochem.*, **6**: 1509 (1975).
33. Tulchinsky, D., Hobel, C. J., Yeager, E., and Marshall, J. R.: Plasma estrone, estradiol, estriol, progesterone and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. *Amer. J. Obstet. Gynecol.*, **112**: 1095 (1972).
34. Valdes Dapena, M. A.: The normal ovary of childhood. *Ann. N.Y. Acad. Sci.*, **142**: 597 (1967).
35. Van Wagenen, G., and Simpson, M.: In: *Postnatal Development of the Ovary in Homo sapiens and Macaca mulatta and Induction of Ovulation in the Macaque*, p. 1 (Yale University Press, New Haven, Conn., 1973).
36. Vermeulen, A., and Verdonck, L.: Radioimmunoassay of 17 β -hydroxy-5 α -androstane-3-one, 4-androstene-3, 17-dione, dehydroepiandrosterone, 17-hydroxyprogesterone and progesterone and its application to human male plasma. *J. Steroid Biochem.*, **7**: 1 (1976).
37. Winter, J. S. D., Faiman, C., Hobson, W. C., Prasad, A. V., and Reyes, F. I.: Pituitary-gonadal relations in infancy. I. Patterns of serum gonadotropin concentrations from birth to four years of age in man and chimpanzee. *J. Clin. Endocrinol. Metab.*, **40**: 545 (1975).
38. Winter, J. S. D., Hughes, I. A., Reyes, F. I., and Faiman, C.: Pituitary-gonadal relations in infancy. 2. Patterns of serum gonadal steroid concentrations in man from birth to two years of age. *J. Clin. Endocrinol. Metab.*, **42**: 679 (1976).
39. Youssefnejadian, D., and David, R.: Early diagnosis of congenital adrenal hyperplasia by measurement of 17-hydroxyprogesterone. *Clin. Endocrinol.*, **4**: 451 (1975).
40. Youssefnejadian, E., Florensa, E., Collins, W. P., and Sommerville, I. F.: Radioimmunoassay of 17-hydroxyprogesterone. *Steroids*, **20**: 773 (1972).
41. The trivial names and abbreviations used are: 17-OH-progesterone, 17 α -hydroxy-4-Pregnene-3,20-dione; testosterone, 17 β -hydroxy-4-Androsten-3-one; Δ^4 -androstenedione, 4-androstene-3,17-dione; progesterone, 4-pregnene-3,20-dione; estradiol, 1,3,5(10)-estratriene-3,17 β -diol; 17-OH-pregnenolone, 3 β -17 α -dihydroxy-5-pregnen-20-one; dehydroepiandrosterone, 3 β -hydroxy-5-androsten-17-one.
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