Thoughts on puberty. The gonads.

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Summary. Adult-type gonadal response to gonadotropins is acquired at the same stage of gonadal evolution in different species, but is not related to either birth or puberty. The critical stage in the ovary is the appearance of the first true antral follicles at about 2 1/2 weeks after birth in rats and mice, 3 weeks in hamsters, and 2 1/2 months in rabbits and sows. However, when this stage is reached the ovary is not always gonadotropin-sensitive. In spite of the presence of antral follicles before birth, gonadotropins have practically no effect on the ovary up to 20 days after birth in ewes, and during at least one year in women. There is no comparable reference point in the testis. However, gonadal maturation appears to occur at the same moment in males and females of the same species. There are two plausible explanations for gonadal non-responsiveness to gonadotropins, although the gonads have apparently reached a sufficient degree of differentiation to respond:

1) the intervention of a factor, possibly of epiphyseal origin, which would inhibit gonadotropic action on the gonads. Although hypothetic, such a factor may possibly play a role in human children during the first months after birth;
2) an inadequate number of specific gonadotropin receptors on target cells. Studies on the testosterone secretion of young rats have shown that this hypothesis may be a reality.

In all mammals studied, the injection of gonadotropins sometime before the normal age of puberty induces ovulation in the female and spermatogenesis in the male. Gonad maturation does not thus seem to be a determining factor in the onset of puberty. However, the gonads cannot respond as adult organs to gonadotropin stimulation until they have reached a certain stage of development. The timing of this, relative to birth, varies a great deal from one species to another. Therefore, in order to understand the puberal process, we must study the evolution of the response of the gonads to gonadotropins, from the formation of those organs during fetal life up to puberty.

Gametogenesis

a) The ovary

Oogenesis (meiotic prophase and primordial follicle formation) is not gonadotropin-dependent. There is no relation between the evolution of the fetoneonatal

However, gonadotropins seem prerequisite to the normal evolution of follicles which are beginning growth. In the ovary of the very young female, the somatic cells do not organize to form the granulosa and theca. Gonadotropins, and particularly FSH, are indispensable to the normal organization of the first follicles (mice : Eshkol et al., 1970 ; Baker and Neal, 1973 ; Eppig, 1977 ; hamster : Challoner, 1975). In the hypophysectomized adult female, follicles begin growth and reach a subnormal preantral stage. However, FSH is necessary for the normal growth of small follicles (hamster : Chiras and Greenwald, 1978). This difference between the adult and the fetus or neonate may be due to the role played by gonadotropins in the differentiation of ovarian interstitial tissue. The interstitial tissue is practically absent in the ovaries of the anencephalic fetus (Ch’in, 1938), and the injection of anti-gonadotropic serum inhibits its development (mouse : Stegner et al., 1970), while gonadotropin injection stimulates it (mouse : Ben-Or, 1970 ; guinea-pig : Aron, 1932, 1933). More precisely, when the pituitary is missing, the rete ovarii is absent or degenerate (macaque : Gulyas et al., 1977), but its cells must be present for normal follicular development (mouse : Byskov, 1974).

In normal young, as long as the first follicles beginning growth have not attained a

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**FIG. 1.** — Evolution of ovarian function from fetal life to puberty.

- Period of oogonial multiplication.
- Period of oogenesis. Meiotic prophase and constitution of primary follicle stock.
- Cl : Onset of growth of first follicles from the stock.
- A : Appearance of first antral follicles.

There is no constant relation between evolution of the gonadotropic function and that of ovarian function during feto-neonatal life in the species studied.

— : Profile of circulating LH evolution for species in which pertinent data are available.

true preantral stage with normal development of granulosa and theca layers (rat: Picon, 1956), exogenous gonadotropin injection does not stimulate final growth and ovulation. The same situation is observed in the adult, i.e. only the follicles reaching preantral stage can be stimulated to ovulate by exogenous gonadotropins (see Thibault and Levasseur, 1979). In all species in which folliculogenesis does not begin until after birth, exogenous gonadotropin injection induces ovulation (or at least considerable development of Graafian follicles) only when the first follicles beginning growth have reached the true preantral stage (around 2 1/2 weeks, rat, mouse: Picon, 1956; Zarrow and Wilson, 1961; 3 weeks, hamster: Bodemer et al., 1959; Greenwald and Peppler, 1968; 2 1/2 months, rabbit: Fox et al., 1964; Aron, 1932; sow: Casida, 1935).

When the first follicles initiating growth reach the preantral stage towards the end of fetal life (fig. 1) (woman, macaque, cow, ewe, guinea-pig), it would appear that they have also attained the developmental stage necessary for them to respond to gonadotropic stimulation by antrum formation and ovulation. Thus, gonadotropic injection in calf causes Graafian follicle development and ovulation in the first week after birth (Marden, 1953). On the other hand, in spite of the presence of antral follicles in 135-day old lamb fetus, exogenous gonadotropin injection is practically without result on the ovary before 20 to 25 days after birth (Mansour, 1959; Mauléon, 1969), and gonadotropins then cause considerable follicular development. In spite of the presence of antral follicles in guinea-pig at birth, exogenous gonadotropin injection has no effect on the ovary during the first 2 weeks of life (Aron, 1932).

The example of the ewe and the guinea-pig demonstrates that when this follicular stage of development is reached, ovarian insensitivity may be prolonged by some other mechanism as an extra precaution against a too early ovarian activity. However, gonadal inactivity before puberty is not always insured: progesterone-secreting corpora lutea as well as large antral follicles are found in the giraffe at the end of fetal life (Kayanja and Blankenship, 1973; Gombe and Kayanja, 1974).

During ovarian development, the appearance of the first true antral follicles determines the time when the ovary becomes gonadotropin-sensitive like an adult ovary. This critical stage is reached at variable times during development in relation to normal age at puberty. In the hamster, the first antral follicles appear at 22 to 23 days, and it is at 22 to 23 days that the classical PMSG-HCG gonadotropin treatment induces the first ovulations 4 days later (Bodemer et al., 1959); the first spontaneous ovulations occur at 29 to 30 days (Greenwald and Peppler, 1968). On the contrary, in woman the first antral follicles appear at 7 to 8 months of fetal life (Pryse-Davies and Dewhurst, 1971) and the first spontaneous ovulations do not occur before 13 to 14 years of age. While the puberal age of the young female depends greatly on her growth rate, the appearance of the first antral follicles on the ovary does not rely on this rate; it is entirely age-dependent (rabbit: Aron, 1932).

b) The testis

In the fetal testis the formation of seminiferous cords and the multiplication of supporting and germ cells can occur without gonadotropins; the seminiferous cords appear sub-normal in lamb fetus decapitated at 50 days of gestation (Courot, 1971) and
in anencephalic human fetus (Ch’in, 1938; Zondek and Zondek, 1965) or hypophysectomized macaque fetus (Gulyas et al., 1977), and gonadotropin injection does not modify them (guinea-pig: Aron, 1933). The aspect of the seminiferous cords is very similar in all mammals at birth, while the evolution of the gonadotropic function is found at very different stages in various species (fig. 2).

**FIG. 2. — Evolution of testicular testosterone secretion and of LH secretion from fetal life to onset of puberal period.**

SD : Sexual differentiation; LH : Circulating LH; T : Circulating testosterone (increasing levels depart from abscessa).

As far as spermatogenesis is concerned, the gonadotropic sensitivity of the seminiferous cords is acquired before puberty since gonadotropin injection may hasten the onset of spermatogenesis (Courot et al., 1970; Courot, 1971; Ortavant et al., 1977). The transformation of supporting cells into Sertoli cells, the first sign of seminiferous cord maturation, relies on gonadotropins, and especially on FSH (mouse: Bressler, 1976; rat: Fritz et al., 1978); the injection of FSH and LH induces the onset of spermatogenesis (lamb: Courot, 1971). However, at present there seems to be nothing indicating at what moment the seminiferous cords become functional under gonadotropic action. Testis gonadotropin sensitivity may appear at the same time as in the ovary. In fact, exogenous gonadotropins have no action on spermatogenesis in the 1 to 2-month old male rabbit (Aron, 1932), whereas in the doe-rabbit, ovary sensitivity appears at 2 1/2 months.

**Steroidogenesis**

Steroid secretion is a basic gonad activity.

a) The testis. — In all mammals studied, the testis secretes testosterone as soon as it is formed, often even before the sex of the gonad can be easily determined and before fetal gonadotropin secretion begins. The ability to secrete testosterone is evidenced *in vitro* in an anhormonal medium (rabbit: George et al., 1978). However, as soon as they differentiate, the interstitial cells (Leydig cells) causing this secretion respond to gonadotropic hormones, and particularly to LH. LH receptors appear on the leydig cells when the fetal testis begins to secrete testosterone (rabbit: Catt et al., 1975); LH or cAMP *in vitro* increases fetal testis testosterone production (man: Ahluwalia et al., 1974; rat: Picon, 1976; Picon and Ktorza, 1976; rabbit: George et al., 1978). When fetal gonadotropin secretion begins shortly after sexual differentiation, testis testosterone secretion follows the evolution of LH secretion (fig. 2). When the functional pituitary is ablated, the interstitial tissue is abnormal and testosterone is no longer secreted (lamb: Courot, 1971; human anencephalics: Zondek and Zondek, 1965). When fetal gonadotropin secretion commences well after sexual differentiation, the interstitial tissue, after considerable transitory activity, regresses and testosterone secretion only re-commences when gonadotropic activity is established (fig. 2).

Testis maturation is completed when under gonadotropic effect, not only steroidogenic but gametokinetic functions are stimulated. This important stage of testicular development may depend on the evolution of the interstitial tissue. In fact, pig Leydig cells secreting testosterone during feto-neonatal life are essentially intertubular cells, while at the onset of puberty the peritubular cells are the more prominent (Van Straten and Wensing, 1978). As an analogy with ovary evolution (see below), it is tempting to postulate a relation between testis maturation and the steroidogenic activity of interstitial cells in close contact with the seminiferous tubules.

b) The ovary. — It was believed for a long time that the female was characterized by the absence of ovarian steroid activity during feto-neonatal life. However, it
appears that while the fetal ovary, when formed, does not secrete testosterone, it can synthesize estradiol from acetate or cholesterol (rabbit: Milewich et al., 1977; George and Wilson, 1979; ewe: Mauléon et al., 1977; cow: Shemesh et al., 1978). This early steroidogenic activity is transitory; it ceases before the beginning of oogenesis (ewe: Mauléon et al., 1977; cow: Shemesh et al., 1978; rabbit: George and Wilson, 1979). Steroid secretion, and particularly that of estradiol, can only re-commence when the true antral follicles appear in the ovary. Estradiol secretion is then gonadotropin-dependent and is insured by the collaboration of the internal theca secreting testosterone and the granulosa aromatizing it (see Thibault and Levasseur, 1979).

In sow, ovarian estradiol secretion begins to increase at about week 11 after birth when the first antral follicles appear (Schlenker et al., 1973). In cow (Challis et al., 1974) and macaque (Resko, 1974), estradiol secretion is higher in female fetuses at the end of gestation when antral follicles are present in the ovary. However, this estradiol secretion remains at a low level. Gonadotropin secretion is low in most of the species studied at the time the antral follicles appear on the ovary and up to puberty (fig. 1). This would explain the low steroidogenic activity of the ovary before puberty.

However, there are exceptions to these observations. Antral follicles are present on woman’s ovary at birth (Peters et al., 1976), and in young humans gonadotropin secretion is high for several months after birth before damping during infancy (fig. 1). This large gonadotropin secretion induces ovarian estradiol secretion (Bidlingmaier et al., 1974) but at a very low level when compared to the secretion triggered by the same gonadotropin levels in the adult (fig. 3). Testosterone secretion is also very low (Forest et al., 1974).

In this case again, it has to be granted that the ovary has become practically

![Graph](image_url)  
**FIG. 3.** — Evolution of LH, FSH and estradiol secretion in the little girl after birth.  
Comparison with LH, FSH and estradiol levels in woman in follicular phase.  
insensitive to gonadotropins due to some other mechanism. This mechanism only seems to be effective for a rather short time as true early puberty has been described in girls before the age of 5 years (Donovan and Van der Werff ten Bosch, 1965) *.

Non-steroidogenic factors of gonadal origin

It is now well established that gonadotropin secretion in the adult is controlled by gonadal steroids and by a non-steroidogenic factor of gonadal origin called « inhibin » in the male. This factor mainly directs FSH secretion in the male and the female (Baker et al., 1976 ; Welschen et al., 1977). It is secreted by the Sertoli cells in the male (Steinberger and Steinberger, 1976), and is present in the follicular fluid of the female (Welschen et al., 1977 ; Marder et al., 1977). Even when they have low steroidogenic and gametokinetic activity, the gonads may secrete a non-steroidogenic factor acting on gonadotropin secretion well before puberty.

a) The testis. — Cryptorchidism in the adult causes a rise in FSH secretion because the Sertoli cells present abnormal secretory activity (man : Chemes et al., 1977 ; rat : Rich and de Krester, 1977). Even before the Sertoli cells differentiate in the young, cryptorchidism has already affected FSH secretion. In the cryptorchidic lamb FSH secretion reaches a higher level than in normal young at 5 weeks, while the onset of spermatogenesis only occurs at about 11 weeks (Blanc and Terqui, 1976). In man, although FSH secretion is identical between 1 and 11 months in babies with cryptorchidism and normal babies (Job et al., 1977), FSH secretion is higher in cryptorchidic children 4 to 5 years old than in normal subjects of the same age (Sizonenko et al., 1978).

b) The ovary. — In dysgenetic girls, postnatal repression of the hypothalamo-pituitary gonadotropic function characterizing infancy (Levasseur, 1977) only becomes evident at 3 to 4 years (Grumbach et al., 1974 ; Conte et al., 1975). In normal girls, gonadotropin secretion is strongly and abruptly reduced at 5 to 6 months after birth (fig. 4). Since ovarian steroidogenic activity is low in these little girls, the difference noted between the evolution of gonadotropin secretion in a normal ovary and in an abnormal one may implicate a non-steroidogenic secretion of ovarian origin, capable of inhibiting gonadotropin secretion.

Discussion

The study of the evolution of the gonads from their formation during fetal life shows that :

1) there is a stage of critical development during which they can theoretically respond to gonadotropin stimulation as adult gonads ; this is marked by the appea-

* It is usually related to the presence of a pituitary hamartoma which we now know secretes GnRH (Judge et al., 1977).
rance of the first true antral follicles in the ovary and perhaps peritubular Leydig cell activation in the testis;  

2) when hypothalamo-pituitary activity and the state of the gonads in the same species are compared, it is evident that there are stages during which the gonads remain silent, despite the fact that they have apparently reached a sufficient degree of differentiation to respond. Two explanations are plausible:

a) The intervention of a factor inhibiting gonadotropin action on the gonads.

The inhibitory role of the epiphysis on the sexual function has often been mentioned in the literature on puberty. A polypeptide has been isolated in the epiphysis or in urine from which it disappeared after epiphysectomy (Ota et al., 1971). When injected into adult or immature rats or mice, it has anti-gonadotropic effects. This polypeptide does not prevent the rise of circulating gonadotropins after castration (Berthelay et al., 1976), but delays it (Damian et al., 1977, 1978). However, it does prevent compensatory ovarian hypertrophy after hemi-castration (Berthelay et al., 1974) or the induction of ovulation with PMSG + HCG (Ota et al., 1970). If this factor could be isolated in young mammals at a time when its action would be most likely to intervene, the role of the epiphysis might be clarified. This would be the case in humans during the first months after birth when LH and FSH secretion is important. During that time in male babies, testis testosterone secretion is abundant (Forest et al., 1973, 1976), although spermatogenesis is not triggered in the seminiferous tubules (Mancini et al., 1960), and in female babies ovarian steroidogenic activity is very low.

Estradiol secretion and compensatory ovarian hypertrophy after castration mainly depend on FSH, and the initiation of spermatogenesis on the combined action of FSH and LH; thus, the most likely hypothesis is a specific suppression of FSH activity since the LH-dependent secretion of testosterone is not inhibited.
b) An inadequate number of specific gonadotropin receptors on target cells.

LH-dependent testosterone secretion is a good illustration of this situation. Testosterone secretion in rats increases during the puberal period concomittantly with the augmentation in the number of testicular LH receptors (Ketelslegers et al., 1978). This increment has no relation to the pattern of LH secretion, but is closely linked to the increase of FSH secretion (Ketelslegers et al., 1978). As FSH injections cause an increase in the number of testicular LH receptors and of testosterone secretion under LH effect (Odell and Swerdloff, 1976; Chen et al., 1977), testicular sensitivity to LH for testosterone secretion seems to mainly depend on FSH. The latter thus always appears as a key-hormone in gonadal activity.

This conclusion is confirmed in calves. The increment in testosterone secretion during the puberal period only begins at about 5 months and is unrelated to LH secretion, which is considerable since the age of 2 months (Lacroix et al., 1977). The increment in testosterone secretion, however, seems to occur concomittantly with the increment of FSH (Karg et al., 1976), as in rats.

Finally, the example of the ram-lamb indicates that the gonad itself may be responsible for the progressive appearance of its own sensitivity to LH. This is suggested by the early gonadal secretion of a non-steroidogenic factor limiting gonadotropin secretion, and particularly FSH.

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Résumé. La réponse de type adulte des gonades aux gonadotropines est acquise à un moment comparable de leur évolution dans les différentes espèces, mais qui n’est lié ni à la naissance, ni à la puberté.

Pour l’ovaire, le stade critique est l’apparition des premiers vrais follicules à antrum, vers 2,5 semaines après la naissance chez la ratte et la souris, 3 semaines chez le hamster, 2,5 mois chez la lapine et la truie. Pourtant, lorsque ce stade critique est atteint, l’ovaire ne répond pas toujours aux gonadotropines : malgré la présence de follicules à antrum avant la naissance, les gonadotropines sont pratiquement sans action sur l’ovaire jusqu’à 20 jours après la naissance chez la brebis et pendant au moins un an chez la femme.

Pour le testicule, il n’existe pas actuellement de point de repère comparable. Il semble cependant que la maturation de la gonade se situe au même moment chez le mâle et la femelle de la même espèce.

Deux causes peuvent être invoquées pour expliquer l’insensibilité aux gonadotropines de gonades qui semblent avoir atteint leur état de différenciation critique : 1) l’intervention d’un facteur inhibant l’action des gonadotropines, qui pourrait être d’origine épiphysaire. Hypothétique, l’intervention d’un tel facteur apparaît possible chez l’enfant humain dans les mois qui suivent la naissance ; 2) l’insuffisance du nombre de récepteurs spécifiques des gonadotropines sur les cellules cibles. La réalité de cette cause d’insensibilité apparaît bien dans l’étude de la sécrétion de testostérone chez le jeune rat.
References


