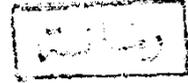بسم الله الرحمن الرحيم

Amenorrhea

Essay

Submitted for partial fullfilment of master degree in ob -
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الله

بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ.

صَدَقَ اللهُ الْعَظِيمُ
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Contents

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(I) PHYSIOLOGY OF MENSTRUATION

Diagnosis and management of abnormal menstrual function must be based upon an understanding of the physiologic mechanisms involved in the regulation of the normal cycle.

Dynamic relationships exist between the pituitary and gonadal hormones which allow for the cyclic nature of normal reproductive processes.

These hormonal changes are correlated with morphologic changes in the ovary, making the coordination of the system one of the most remarkable events in biology.

The menstrual cycle can be best described by dividing the cycle into three phases: The follicular phase, ovulation and the luteal phase.

(A) The Follicular phase:

During the follicular phase an orderly sequence of events takes place which ensures that the proper number of follicles is ready for ovulation.

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In the human ovary the end result of this follicular development is (usually) one surviving mature follicle. This process, which occurs over the space of 10-14 days, features a series of sequential actions of hormones on the follicle, leading the follicle destired to ovulate through a period of initial growth from a primordial follicle through the stages of the preantral, antral and preovulatory follicle.

The primordial follicle consists of an oocyte, arrested in the diplotene stage of meiotic prophase, surrounded by a single layer of granulosa cells.

Until their numbers are exhausted, follicles begin to grow under all physiologic circumstances. Growth is not interrupted at all ages, including infancy and around the menopause.

The number of the follicles which starts growing each cycle is probably dependant upon the size of the residual pool of inactive follicles. (Peters et al. 1975).

* The preantral follicle:

Once growth is initiated, the follicle progresses to the preantral stage as the oocyte enlarges and is surrounded by a membrane, zona pellucida.

The granulosa cells undergo multilayer proliferation as thecal layer begins to organize from the surrounding stroma. This growth is dependant upon gonadotropins and is correlated with increasing production of estrogen.

The granulosa cells of the preantral follicle have the ability to synthesize all three classes of steroids, however, significantly more estrogens than either androgens or progestins are produced. An aromatase enzyme system acts to convert androgens to estrogens and appears to be a factor limiting ovarian estrogen production. Aromatization is induced or activated through the action of FSH. Specific receptors for FSH are present on preantral granulosa cells and (in the presence of FSH) the preantral follicle can aromatize limited amounts of androgens and generate its own estrogenic microenvironment. (Mc Natty et al. 1979).

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Estrogen production is, therefore, also limited by FSH receptor content. The administration of FSH will raise the concentration of its own receptor on granulosa cells both in vivo and invitro (Richards J.S. 1979).

In addition, FSH combines with estrogen to exert a mitogenic action on granulosa cells to stimulate their proliferation. The fate of the preantral follicle is in delicate balance. At low concentrations, androgens enhance their own aromatization and contribute to `estrogen production. At higher levels, the limited capacity of aromatization is overwhelmed and the follicle becomes androgenic and ultimately atretic.

Perhaps follicles will progress in development only if emerging when FSH is elevated and LH is low. The success of a follicle depends upon its ability to convert an androgen microenvironment to an estrogen microenvironment.

* **The antral follicle:**

Under synergistic influence of estrogen and FSH there is an increase in the production of follicular fluid which accumulates in the intercellular spaces of

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the granulosa, eventually coalescing to form a cavity, as the follicle makes its gradual transition to the antral stage. The accumulation of follicular fluid provides a means whereby the oocyte and surrounding granulosa cells can be nurtured in a specific endocrine environment for each follicle.

FSH is detectable in follicular fluid when estrogen concentrations exceed those of androgens. Conversely , in the absence of FSH, androgens predominate (Mc Natty et al 1980). LH is not normally present in follicular fluid until, or just, after the midcycle surge.

If LH is prematurely elevated in plasma and antral fluid, mitotic activity in the granulosa decreases, degenerative changes ensure, and intrafollicular androgen levels rise. Therefore, the presence of estrogen and FSH in antral fluid is essential for sustained accumulation of granulosa cells and continued follicular growth.

The steroids present in follicular fluid can be found in concentrations often several orders of magnitude higher than those in plasma reflecting the functional capacity of the surrounding granulosa and

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thecal cells. The synthesis of steroids hormones is functionally compartmentalized within the follicle - the two - cell mechanism.

In the antral follicle, LH receptors are present only on the thecal cells and FSH receptors only on the granulosa cells. The interaction between the granulosa and thecal compartments, with resulting accelerated estrogen production, is not fully functional until later in antral development. (Erickson G.F. 1986), (Erickson et al., 1985), (McNatty et al., 1979), (Hillier et al., 1981).

The successful conversion to an estrogen dominant follicle marks the "Selection" of a fallicle distined to ovulate, a process whereby, (with rare exception) only a single follicle succeeds. This selection process is the result of two estrogen actions:

(1) A local interaction between estrogen and FSH within the follicle.

(2) The effect of estrogen on pituitary secretion of FSH. While estrogen exerts a positive influence on FSH action within the maturing follicle, its negative feed back relationship with FSH at the

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hypothalamic – Pituitary level serves to withdraw gonadotropin support from the other less developed follicles (Hillier et al., 1981).

The fall in FSH leads to a decline in FSH dependant aromatase activity, limiting estrogen production in the less mature follicles even if a lesser follicle succeeds in achieving an estrogen environment, decreasing FSH support would interrupt granulosa proliferation and function, promote a conversion to an androgenic microenvironment, and thereby indue irreversible atretic change. Indeed, the first event in the process of atresia is a reduction in FSH receptors in the granulosa layer.

An asymmetry in ovarian estrogen production, an expression of the emerging dominant follicle, can be detected in ovarian venous effluent as early as cycle day 5-7, corresponding with the gradual fall of FSH levels observed at mid follicular phase. (Chikasawa et al., 1986). Because the lesser follicles have entered the process of atresia, loss of the dominant follicle during this period of time requires begining over, with recruitment of another set of preantral follicles. (Dizerega et al., 1981).

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The negative feedback of estrogen on FSH serves to inhibit the development of all but the dominant follicle, but the selected follicle remains dependant on FSH and must complete its preovulatory development in the face of declining plasma levels of FSH.

The dominant follicle has a significant advantage, a greater content of FSH receptors a acquired because of a rate of granulosa proliferation that suppresses that of its cohorts. As a result, the stimulus for aromatization, (FSH) can be maintained, while at the same time it is being withdrawn from among the less developed follicles. A wave of atresia among the lesser follicles is therefore seen to parallel the rise in estrogen.

In order to respond to ovulatory surge and to become a successful corpus luteum, the granulosa cells must acquire LH receptors. FSH induces LH receptor development on the granulosa cells of the large antral follicles. Here again estrogen serves as the chief coordinator, with increasing estrogen concentrations within the follicle, FSH changes its focus of action, from its own receptors to LH receptor.

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The pattern of gonadotropin secretion observed in the menstrual cycle is the result of feedback modulation of steroids originating in the dominant follicle, acting directly on the ant. pituitary.

Experimental evidence suggests that the estrogen positive feedback mechanism involves an increase in GnRH receptor concentration, while the negative feedback action operates through a different and certain system. (Adams et al., 1981).

Estrogen exerts its inhibitory effects in both the hypothalamus and the anterior pituitary, decreasing both GnRH seretion and response. (Chappel et al., 1981). Progesterone also operates in two sites, its inhibitory action is at the hypothalamic level, and like estrogen, its positive action is directly on the pituitary. (Wildet et al., 1981).

* **The Preovulatory follicle:**

Granulosa cells in the preovulatory follicle and acquire lipid inclusions while the theca becomes vaculated and richly vascular, giving the preovulatory follicle a hyperemic appearance.

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