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Steroidal Hormonal Contraceptive Agents

甾体激素避孕药

Selected Papers on Planned Parenthood

Vol. 4

Steroidal Hormonal Contraceptive Agents

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Abstracts
摘　要

本文综述了月经周期中子宫内膜的变化，讨论了控制月经的内分泌因素，并概述了正常月经周期中激素的变化及其生理意义。文中较详细地介绍了 Markee 将子宫内膜组织移植于猴眼前房直接观察的工作。

本文综述了正常月经周期中卵巢形态与激素的周期性变化。作者将周期中的形态学变化分为四个时相：1)初级的卵泡生长，2)卵泡的成熟与闭锁，3)排卵期，4)黄体化与黄体。将周期中的激素变化也分为四个时相：1)初级的卵泡生长，2)卵泡成熟与闭锁、溢体生成，3)排卵期，4)黄体的生命和死亡。文中引用了大量实验资料，作了较为详尽的叙述。

文章的最后部分简单地介绍了一种新的研究途径：考虑到月经周期的调节非常复杂，其正常功能有赖于许多变数的相互作用，作者发展了一种月经周期的工程分析，用非线性的代数学和微分方程，明确地描述周期中各个激素与形态成分的特性。

哺乳类动物的排卵过程（分反射性和自发性二种）均受神经内分泌的控制，其中包括丘脑对垂体和卵巢功能的影响以及血中促性腺激素和卵巢激素在血中浓度的变化对丘脑和垂体的反作用，即所谓垂体功能的反馈调节，它促进或抑制排卵过程，并造成灵长类动物正常的月经周期。克罗米芬诱发排卵和甾体类避孕药抗排卵的作用机制都是由于影响了这种反馈机制，其主要作用部位是在丘脑。

文章首先描述观察指标的标准。详细介绍正常月经周期和短月经周期中的 FSH 和 LH 的曲线变化，以及相应的 17-羟基黄体酮、黄体酮、基础体温的变化。

文中比较了正常周期与短周期之间 FSH、LH，以及两者的分泌特点和比率上的差异。作者在文中还暗示 17-羟基黄体酮作为观察指标的意义。

最后作者阐述了 F 丘脑、垂体、性腺激素之间的调节关系，也讨论了目前测定性激素、FSH 和 LH 方法上存在的一些问题。

本文综述了兔精子获能与各种激素之间的关系。扼要叙述了促性腺激素对兔精子获能的影响；精子在动情、去卵巢与假孕兔子宫内的获能；精子在孕激素处理过的兔子宫内的获能等。尽管不同作者所得实验结果不一致，但有许多证据支持精子在假孕或孕酮处理过的兔子宫内的获能受到抑制的观点。此外，兔精子在输卵管内获能，不论在假孕兔或在去卵巢而用雌激素或孕酮处理过的兔上均可完成，但在去卵巢而不给予激素处理的兔上则不能完成。不过这些报告尚有待重复。作者主张在人和其它动物上进一步研究精子获能的激素调节。

发病率高于序贯用药者。17.9%的闭经者合并乳溢 (Galatorrhea)，这些患者中脑垂体肿瘤的发病率在上升。内腔镜检查，如果卵巢已呈现为硬化囊性状态，治疗效果较正常卵巢或多囊卵巢为差。

在治疗及预后上，黄体酮撤退性试验是个重要步骤，注射黄体酮后出现撤退性流血者，可以应用 Clomid 治疗，每月剂量可由 50 毫克/日 × 5 天增加到 200 毫克/日 × 5 天，直到出现排卵。如无撤退性流血，则首先进行 1～2 个月雌激素-黄体酮的周期性治疗，而后应用 Clomid，并可考虑应用皮质激素、绒毛促性腺激素。本组 24 例希望生育者经过治疗，12 例受孕。

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口服合并式雌一孕激素避孕药与色氨基酸和维生素 B_6 代谢异常之间的关系，前已有所报导。本文对 22 例精神抑郁妇女(估计其发病原因系由于服用避孕药所引起)进行了研究。生化测定结果发现维生素 B_6 完全缺乏者有 11 例。本组妇女在双育交叉试验中对应用维生素 B_6 的临床反应良好。另外 11 例则无如此反应。服用安慰剂者并无作用。作者讨论了有关口服避孕药产生精神抑郁症的可能机制及维生素 B_6 的治疗问题。

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用避孕药具的妇女中癌前期宫颈损伤的早期发生率

本文是纽约计划生育联合门诊对妇女中子宫颈癌前期发生与不同避孕药具关系的进一步研究。在初步研究中曾报导了应用甾体药物避孕妇女的癌前期发病率稍高于应用阴道隔膜妇女。进一步研究目的在于观察延长使用各种避孕药具后子宫颈癌前期的发病情况。

在研究中该联合门诊对每一个节育妇女详细询问病史；包括年龄，种族、初产年龄、生育次数、家庭经济等项目；并作全身和阴道细胞学检查。在 78098 节育妇女中选择了 13018 人应用甾体避孕药，阴道隔膜或宫内节育器者，其中有 7704 人连续 2 年阴道细胞学阴性定为配对统计分析对象：甾体药物 3045 人和阴道隔膜 1015 人配对，比例为 3:1。甾体药物 2733 人和宫内节育器 911 人配对，比例为 3:1。

统计结果表明应用甾体药物避孕的原位癌和癌前期的发病率和应用阴道隔膜或宫内节育器的原位癌和癌前期的发病率无统计学上有意义数的区别。同时在这次研究中，也未发现由于应用避孕药具导致癌前期和癌的发病率的增加。

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Physiology of Reproduction

PHYSIOLOGY OF MENSTRUATION

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THE MENSTRUAL CYCLE AND ITS ASSOCIATED features profoundly affect many facets of female behavior. Besides the overt signs and symptoms of menstruation, subtle influences may relate female reproductive aspirations and apprehensions to the menstrual cycle. These interactions serve to emphasize the pervasive authority exercised by the reproductive cycle and by menstrual function.

Menstruation follows the withdrawal of hormonal support from the uterine endometrium with consequent bleeding. The state of the endometrium thus reflects the controlling influence of ovarian hormones. Although a relationship between ovarian function and menstruation was speculated upon in 1793 (10), it was not until the mid-nineteenth century that investigations of the reproductive cycles in lower animals were undertaken. Discovery of the mammalian ovum in 1827 by von Baer, the prominent zoologist, started an enthusiastic exploration of reproductive physiology (19), but the basic concepts of menstruation in the human and subhuman primate were not unraveled for another hundred years. The framework of our current understanding of cyclic endometrial changes was built by the pioneering work of such invesigators as Allen, Bartelmez, Corner, Hartman, and Markee (2,3,4,5,7,9,10,13,20,21).

In this article we will: 1. Review the changes in the uterine endometrium leading to menstruation; 2. Discuss endocrine factors which govern the process of menstruation; and 3. Outline hormonal changes occurring during the normal menstrual cycle and their physiologic significance, to provide a background for succeeding discussions on *dysfunctional uterine bleeding* which is characterized by its deviation from the norm.

BACKGROUND

For many years concepts of menstruation in the human were based on extensive work carried out in lower animals. Formulation of present knowledge of menstrual physiology, therefore, was delayed because

species differences are extensive, not only in morphology of the reproductive tract, but also in physiologic patterns of reproduction. For example, the domestic hen ovulates daily, while ovulation in the dog occurs only approximately twice per year during periods of "heat." The rabbit ovulates on response to coitus; ovulation in other species is confined to intervals of increased sexual receptivity during which copulation occurs.

Analogy Between Menstruation and Estrus Cycles in Animals

Formulation of present concepts of menstrual physiology was also restrained by the persistent belief that menstruation in the human female is analogous to periods of estrus in lower forms. While it is true that estrus in certain species and menstruation in the human play a similarly prominent role in the reproductive cycle, menstruation and estrus are now recognized to be quite dissimilar. Periods of estrus or "heat" are intervals of heightened sexual activity with a propensity towards mating. Sexual activity in the human is not restricted to specific times in the cycle so that coitus does not carry the same risk of impregnation that accompanies mating in species with estrus cycles.

Ovulation, the focal point of the reproductive cycle, is common to all mammalian species. Ovum release may occur during estrus, in response to coitus or other stimulation, or, as in the human, periodically without an associated interval of estrus. The onset of estrus is accompanied by changes in the ovaries and follicular ripening. Some species with estrus cycles, such as the guinea pig, do not demonstrate behavioral signs of estrus; however, distinctive cytologic changes in vaginal epithelium can be correlated with particular phases of the ovarian cycle and with periods of estrus. In the rabbit, coitus initiates a series of changes which result in follicular maturation and culminate approximately 12 hours later in ovulation. In the human, however, ovulation does not come about during a period of heightened sexual activity, nor is it a consequence of each act of coitus. In the absence of pregnancy, however, ovulation in the human defines the time of the succeeding menstruation. Thus the prominent features in all mammalian reproduction are the development of the graafian follicle and its accompanying significant changes in the genital tract, ultimate release of the ovum with ensuing establishment of the corpus luteum, and further effects on the reproductive structures brought about by luteal secretions which essentially prepare the uterus for possible nidation.

The details and timing of these events in individual species are related to its particular reproductive mechanism. Care must be exercised in drawing conclusions about these physiologic processes in one species from information on another species. Obviously, the experimental animal lends itself more easily than the human to the extensive investigations required to understand reproductive processes. The experimental animal must be as similar as possible to the human in reproductive habit, and the possible importance of differences must be kept in mind when results are interpreted.

Observations on Menstruation in the Rhesus Monkey

At the turn of the century Walter Heape reported his observations on menstruation and ovulation in the *Macaca rhesus* to the Royal Society of London (15). The report was significant for several reasons: first, his work with the rhesus monkey led Heape to speculate on reproductive cycle similarities between monkey and human; second, at a time when it was generally felt that menstruation and ovulation occurred simultaneously, Heape suggested that this relationship need not hold true. Third, he pointed out that ovulation does not necessarily take place in each menstrual cycle in the monkey, especially during the nonbreeding season, and that anovulatory cycles may also occur in the human. Since further work has confirmed that reproductive cycles in the higher monkeys and the human are similar, the rhesus monkey has been used extensively for studies of menstrual physiology. Corner (8) recognized a temporal relationship between ovulation and subsequent menstruation, with menstruation occurring approximately 12–13 days after ovulation in this species. He also observed that menstruation may occur *without* a preceding ovulation, and suggested a correlation between the premenstrual phase of primates and the postestrus interval of other mammals. Allen's rhesus monkey investigations reported in 1927 form the basis today for the widely held estrogen deprivation theory of menstruation (2). Further work in the same species by Hisaw (16) demonstrated that withdrawal of corpus luteum extracts resulted in uterine bleeding. Hartman (13) subsequently recorded data on over 7000 menstural cycles in the *Macaca rhesus,* with some animals followed for more than 50 cycles. Mastering the technique of bimanual ovarian palpation, he was able to record ovarian dimensions and diagnose the occurrence of ovulation on the basis of his findings. These observations also suggested that although regular alternation of ovulation from one ovary to another was the usual condition, it was not the rule. Similarities

between the reproductive cycle of the human female and that of the subhuman primate have opened the way for additional basic studies in the monkey which could not have been carried out in the human, such as Markee's direct visualization of endometrial tissue transplanted to the anterior chamber of the eye (21) and Sturgis' studies on follicular atresia (31).

Thus, our knowledge of menstrual physiology has developed largely through relatively recent studies, in the rhesus monkey. It must be re-emphasized, however, that any hypotheses concerning menstruation derived from monkey investigations and applied to the human, are conditional on the possibility of significant differences, despite strong interspecies similarities.

PHYSIOLOGY

Cellular regression and replacement are characteristic features of life cycles of most tissues, and the cyclic shedding of the uterine endometrium is one of the most dramatic examples. The human endometrium may undergo growth and proliferation followed by shedding of its superficial portion some 300–400 times during reproductive life! The accompanying bleeding is self-limited and restoration of endometrial integrity begins almost immediately after onset of desquamation. Perhaps the most outstanding contribution to our knowledge of events in the endometrial cycle was provided by Markee (21) in 1940. Transplanting fragments of endometrial tissue to the anterior chamber of the eye of the rhesus monkey, Markee was able to observe the endometrium directly, continuously, and at high magnification. His description of endometrial changes through many cycles is classic both for its ingenious technique and for its invaluable information.

Endometrial Growth Cycle

Four periods in the endometrial growth cycle were recognized, beginning with a resting phase of variable length from the end of the last bleeding phase to the onset of endometrial growth. An initial period of growth lasted 8–15 days, during which some of the ocular transplants increased up to threefold in size. Slight regression occurred at about ovulation time, followed by a second period of growth during which transplanted fragments again doubled or tripled in area. Finally a period of regression decreased transplants to their original size. Bleeding occurred on the second to seventh day of regression when the area occupied by each endometrial fragment had decreased 25–75

per cent. Onset of regression varied from one transplant to another even in the same animal. Although menstruation was always preceded by regressive changes in the endometrium, regression was not always followed by menstruation.

Vascular changes and blood flow

Markee paid particular attention to the vasculature of the endometrium, having previously demonstrated rhythmic fluctuations in endometrial vascularity with blanching before menstruation (20). He observed that regression of the endometrium was preceded by decreased blood flow through endometrial vessels. Two types of arteries were recognized. The basal one-third of the endometrium receives its blood supply from straight, short arteries, while the superficial two-thirds derives its blood supply from coiled vessels. These two types of vessels can be recognized histologically, coiled arteries have thicker walls and a larger diameter. During endometrial growth coiled arteries lengthen, and their rate of linear growth exceeds that at which the endometrium thickens. Consequently, tips of the coiled vessels closely approach the epithelial surface. Similarly, as the phase of endometrial regression begins, thickness of the endometrium diminishes more rapidly than arterial length. Both of these processes result in an increased arterial coiling and a closer proximity of vessels to the endometrial surface.

As a consequence of increased vascular coiling and subsequent compression, the blood flow through coiled vessels is slowed during the phase of endometrial regression. Stasis of flow is accompanied by vasodilatation, varying in incidence, duration and degree. Menstruation usually begins within 4 days of vascular compression. No extravasation of blood occurs during vasodilatation; prior to the onset of menstruation, vasodilatation gives way to a period of vasoconstriction. Coiled vessels which supply blood to the superficial two-thirds of the endometrium contract 4–24 hours prior to bleeding producing ischemia of the superficial portion of endometrium. The straight arteries do not constrict, leaving blood supply to the basal endometrium uncompromised.

During the period of stasis, leukocytes migrate through capillary walls, first into stroma immediately adjacent to the capillary and ultimately into surrounding stroma. Bartelmez (3) considered leukocytic infiltration a constant criterion for histologic diagnosis of "impending menstruation," and even speculated that leukocytes may function to accelerate tissue destruction.

After coiled arteries have been constricted for several hours, blood escapes from their branches. In Markee's ocular transplants 5 types of menstrual bleeding were found: 1. Hemorrhage from hematomata formed after breakage in a capillary or arteriole wall; 2. Direct bleeding from capillaries or arterioles through epithelium without hematoma formation; 3. Diapedesis of blood cells through capillary walls; 4. Venous bleeding from vessels opened by shed tissue; and 5. Secondary bleeding from defects in arteriolar walls.

Little tissue is lost in the first 12 hours, but thereafter tissue fragments become detached and are shed. The amount of tissue lost seems to correlate with the degree of coiling in superficial arteries: the more highly developed the coiled arteries, the more tissue is lost.

Changes in endometrial layers

During an ovulatory menstrual cycle, endometrium may increase in thickness from 0.5–5 mm. or more (4). Loss of thickness during regression and menstruation can be accounted for by dehydration of tissue as well as by tissue loss. A number of investigators have postulated that during menstruation the superficial compact layer of endometrium and the intermediate stratum spongiosum are both completely sheared off, and that regeneration occurs from the basal layer. Bartelmez (4), however, has indicated that some of the spongiosum remains in place and dedifferentiates to reorganize into new epithelium. The persistence of residual tissue superficial to the basal layer is supported by McClennan and Rydell who feel that, in the human, newly regenerated endometrial surface is usually derived from active endometrium which has already participated in secretory activity. Even as late as cycle days 3 and 4, portions of the spongiosum are retained, but McClennan has been unable to find remnants of the stratum compactum during menstruation. Considerable variation, however, can be seen from one uterus to another, as well as in different regions of the same uterus.

In Markee's studies, regeneration of the vascular system is initiated shortly after rupture sites in the coiled arteries are plugged. With relaxation of the basal portions of coiled arteries, blood flow is restored, and new capillaries sprout from the functional zone. The restoration of an adequate circulation may be correlated with termination of menstrual flow.

Cyclic growth and regression associated with periodic menstruation normally persists throughout reproductive life in higher primates, interrupted physiologically only by pregnancy and lactation. As early

as 1897, Heape observed that corpora lutea were *not* present during every menstrual period in the rhesus monkey, and commented that ovulation was *not* a consistent event in every cycle. Corner later confirmed these observations (8) and also found a greater cycle regularity in late winter and spring, with cycles of excessive lengths occurring between June and January. Such observations probably delayed recognition of the now well-recognized temporal relationship between ovulation and menstruation. They may also have provoked Corner's statement that the "occurrence of regular menstruation without corresponding cyclic maturation of follicles and corpora lutea in the ovary is a phenomenon beyond the scope of current theories of ovarian physiology, and offers new complications and difficulties in the way of continued investigation of the primate reproductive cycle." (8) Thus the enigmatic phenomenon of anovulatory cycles was recognized. Markee was able to distinguish only a small number of subtle dissimilarities in the behavior of intraocular implants in ovulatory and in anovulatory cycles. In the ovulatory cycle he noted greater development of coiled arteries, more prominent vasodilatation, closer approximation of coiled arteries to the surface, increased blood loss, more endometrial desquamation and larger shed fragments.

Histological features of endometrial restoration

In the ovulatory cycle, once menstrual flow has started, restoration of endometrium begins. These progressive changes in the human have been described in detail by Noyes, Hertig, and Rock. Proliferative changes characterize the endometrial response to estrogen in the preovulatory phase of the cycle. Initially the surface epithelium is thin, but glands begin to become more tortuous and lining epithelium becomes composed of tall columnar cells. Mitoses can soon be seen in the glandular epithelium; pseudostratification is apparent (Fig. 1A); nuclei of stromal cells seem isolated and stromal mitoses can be recognized. Later in the proliferative phase stroma becomes dense (Fig. 1B) and degree of pseudostratification increases. Following ovulation, endometrial glandular secretory changes begin. Glandular tortuosity increases further, and subnuclear vacuoles can be recognized in the glandular epithelium. The gland nuclei seem pushed to the center of the epithelial cells (Fig. 1C); pseudostratification decreases; and by the third to fourth postovulatory day secretion can be seen in the gland lumina. The vacuoles become displaced to the supranuclear portion of the epithelium. Secretion reaches a maximum approximately 6 days after ovulation (Fig. 1D). By the eighth postovulatory