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VOLUME 10

Research of Contraceptive Agents for Female

女用避孕药的研究

Selected Papers on Planned Parenthood

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Research of Contraceptive Agents for Female

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中 文 摘 要

文中论述，对九种常用口服避孕药片做了生物测定，异炔诺酮 5mg 与乙炔雌二醇三甲醚 75mcg，雌激素作用最强，为乙炔雌二醇 50mcg=1 的强度的 4.88 倍，18 甲基炔诺酮 0.5mg 乙炔雌二醇 50mcg 雌素强度最低为 0.81，二者相差 6 倍。0.00155 微小剂量的雌素强度报导付作用及血栓病较少，孕素对雌素强度的作用，在 18 甲及异炔诺酮完全是附加作用。在炔诺酮、醋炔诺酮与双醋炔诺酮完全是对抗作用，或低浓度加强及高浓度对抗作用。这些结果提示，口服避孕药片安全范围较大，因此孕素与雌素配伍比例可向扩大方向发展。此外口服避孕药片的雌素强度不同，可作为临床需要来选择使用。

本文介绍 18-甲基炔诺酮的放射免疫测定方法，对妇女口服 18-甲基炔诺酮和使用含有 18-甲基炔诺酮的阴道避孕环时，血浆中 18-甲基炔诺酮、黄体酮和雌二醇的水平进行了测定，结果证明阴道环中含有 18-甲基炔诺酮 50 毫克可以完全抑制排卵。

右-18 甲基炔诺酮作为房事后避孕药的临床效果是肯定的，根据 4,631 人次、41,802 周期的总结，失败率为 3.5%，校正失败率为 1.7%。本工作包括 6 名对象，在周期第 12 天，第10和 12 天，第 8、10 和 12 天，以及在 LH 高峰后第 2 和 4 天，第 2、4 和 6 天，每天口服 400

微克。从周期第 8 天起每天测试核固缩指数、宫颈功能、宫颈粘液拉丝度和结晶情况以及雌二醇、孕酮和黄体生成激素的血清含量。结果指出，排卵前服用引起边缘指标的抑制，而且，LH 中期峰受抑制或者降低。在排卵前或排卵后服用对黄体期均未表现干扰。因此，认为这一避孕药的主要作用机理是对经期中边缘功能的抑制。

三个妇女服用 75 微克 18-甲基炔诺酮以后血中药物浓度分别在半小时，2 小时和 3 小时到达 1.5—2 毫微克/毫升、24 小时内降为 0.4 毫微克/毫升。含药的阴道避孕环放入阴道后 24—48 小时血中药物浓度达高峰，15—20 天以后降为高峰值的 30—40%。取环后血浓度很快降低。

本文详细综述了关于长效甲孕酮的性能和安全性。着重报导了甲孕酮肌注剂常用 150 毫克，每三个月一次。其作用方式可能多环节的。根据尿中 LH 和 FSH 测定认为是抑制排卵。其次也可能是使宫颈粘液变稠，于是精子难于穿透。并且影响内膜从而降低胚泡着床率。使用者无妊娠，据报导最高失效率为 1.2%（按妇女年计）。最显著的付反应是闭经，不闭经的对象有不规则出血或出血量较多，这是使对象停药的最大理由。服药对象体重稍有增加。对致癌无确信结论。肾上腺机能不全也无临床证据。发生糖尿症的很罕见。对泌乳量无明显影响。停药几个月后可以恢复正常月经和受精，并无足够例证说明有畸胎影响。

本综述引用了 67 篇有关文章，内容包括以下几个方面：（1）对卵巢的影响，在大多数例子中未看到对滤泡发育的干扰。（2）对血或尿中促性腺激素的影响，结果指出对卵巢、丘脑和垂体均没有表现显著的有害的影响。（3）血中药物含量和无排卵的关系，发现持续闭经和无排卵是由于注射部位吸收缓慢使血液中的药物保持一定含量。（4）停药后排卵和/或生育力的恢复，发现在药物自血液中消失时生育功能即迅速恢复。（5）停药妇女重新妊娠所需的时间，这一方面和用其他方法无差别，而且发现所需的时间与注射的次数无关。

由于不需要每日口服雌激素以抑制排卵，间断脉冲式投药可减少混合型避孕药的付作用而不影响月经正常周期及避孕效果。试验分三组进行，发现每日口服孕激素而隔日口服雌激素可获得最好的周期控制及满意的避孕效果。通过 1090 位妇女试服了 12942 个妇女月，虽有 8 人妊娠，但仅 2 例妊娠是由于服药失败。由于出血付作用，一年停服率为 10.5%。

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THE PHARMACOLOGY OF CONTRACEPTIVE AGENTS

W. D. Odell and M. E. Molitch

Division of Endocrinology, Department of Medicine, Harbor General Hospital, UCLA School of Medicine, Torrance, California

INTRODUCTION

The number of publications on contraceptive and antifertility agents is increasing every year. We have attempted here to review some aspects of the pharmacology and physiology of the agents administered to women. We have avoided discussing minor modifications in dosage or techniques of administration, but instead have concentrated on classes of compounds and selected examples for illustration. We have eliminated discussion of prostaglandins used for abortion and the recent studies of testosterone or androgen treatment of males; the latter has had no clinical trials of contraceptive effectiveness or acceptance. We apologize for these large omissions and our selective view; our task was large and our space limited.

HORMONAL EVENTS DURING THE NORMAL MENSTRUAL CYCLE

A discussion of the mechanism of actions of contraceptive steroids administered to women is most easily understood in context of the physiology of the normal menstrual cycle. Figure 1 depicts the hormonal events occurring during a typical menstrual cycle. These events are centered around ovulation, which is arbitrarily drawn in this figure to occur on day 14 (day 1 is defined as the first day of menstrual flow). In the mature ovary, the primary follicle consists of an oogonium surrounded by a single layer of granulosa cells. Presumably, under the influence of follicle stimulating hormone (FSH), 10 to 15 of these primary follicles undergo development into secondary follicles; the granulosa cells proliferate to several layers thick and the oogonium increases in size during the first few days of the cycle. Through poorly understood local (ovarian) mechanisms, all but one of these secondary follicles undergo atresia and one (normally) is selected for further development. The granulosa cells of the selected follicle continue mitotic division under FSH stimulation, and fluid accumulates between the cells. At the preovulatory stage the follicle is large, and the ovum, called a secondary oocyte at this development stage, projects

into the large fluid-filled antral cavity (1). As this sequence of follicle growth occurs, estradiol concentrations increase in blood, reaching a maximum just prior to the LH-FSH surge (LH = luteinizing hormone). These changes in blood estradiol appear to be predominantly related to changing numbers of granulosa cells.

For a number of years after the development of the competitive binding assay for progesterone, using cortisol binding globulin (CBG) as a binding protein, it was believed that progesterone was secreted in low or undetectable and unchanging concentrations during the follicular phase of the cycle (2–4). CBG has a relatively low affinity for progesterone, and assays using CBG as the binding protein have inadequate sensitivity to quantify progesterone in the concentrations existing during the follicular phase. Many assumed that progesterone could not play any role in control of the process of ovulation. However, studies from our laboratory (5, 6) using more sensitive radioimmunoassays have revealed that progesterone concentrations fall during the first half of the follicular phase and rise again just prior to ovulation as shown in Figure 1. Once the preovulatory follicle has developed and these estradiol and progesterone changes have occurred, a surge of LH and FSH (ovulatory surge) can be detected, followed by ovulation and transformation of the follicle into the corpus luteum. During corpus luteum function, estradiol, progesterone, and other steroids are secreted in large amounts, and blood FSH and LH fall to low concentrations, lower than are observed during the follicular phase (7, 8).

Several facts have led to the conclusion [Odell & Swerdloff 1968 (9)] that timing of ovulation in women is related to an ovarian signal system and is not caused by an inherent central nervous system rhythmicity: (*a*) During carefully studied normal menstrual cycles one does not observe aberrantly timed LH-FSH ovulatory surges (ovulatory LH-FSH surges only occur when a preovulatory follicle is mature); (*b*) during estrogen suppression of castrated or postmenopausal women under defined conditions, rhythmic discharges of LH-FSH are not observed; (*c*) if one were to design a control system for ovulation, the ovarian signal-activated model would be the most efficient indicator, when a mature follicle is developed. To test this postulate, considering ovarian steroids to be the most likely hormonal signals, Odell & Swerdloff (9) administered sequential estrogens and progestogens to castrate and postmenopausal women. The estrogens suppressed elevated FSH and LH concentrations and maintained them at a low level until the progestogen was added. At this time an LH-FSH surge mimicking the ovulatory surge occurred. Subsequent studies by Yen (10) in postmenopausal women and by Weick et al in castrate monkeys (11) have shown that estrogens alone can induce ovalutory LH surges. Schwartz (12) has summarized evidence to indicate that the prime signal in rodents is related to changing estrogen concentrations. Ferin et al (13) have shown that antisera to estradiol, administered just prior to ovulation, blocked the ovulatory LH surge; antisera to progesterone did not block this surge. A review of all animal and human data is consistent with the concept that the changing estrogen concentration is the prime ovarian signal. Thus estrogens may act in two distinct ways upon the central nervous system: 1. in negative feedback to suppress LH and FSH secretion, and 2. in "positive feedback" to stimulate LH secretion. Whether the negative or the positive action is expressed, appears to be dependent on change and dose of estrogen and the presence or absence of other hormones such as progestogens.

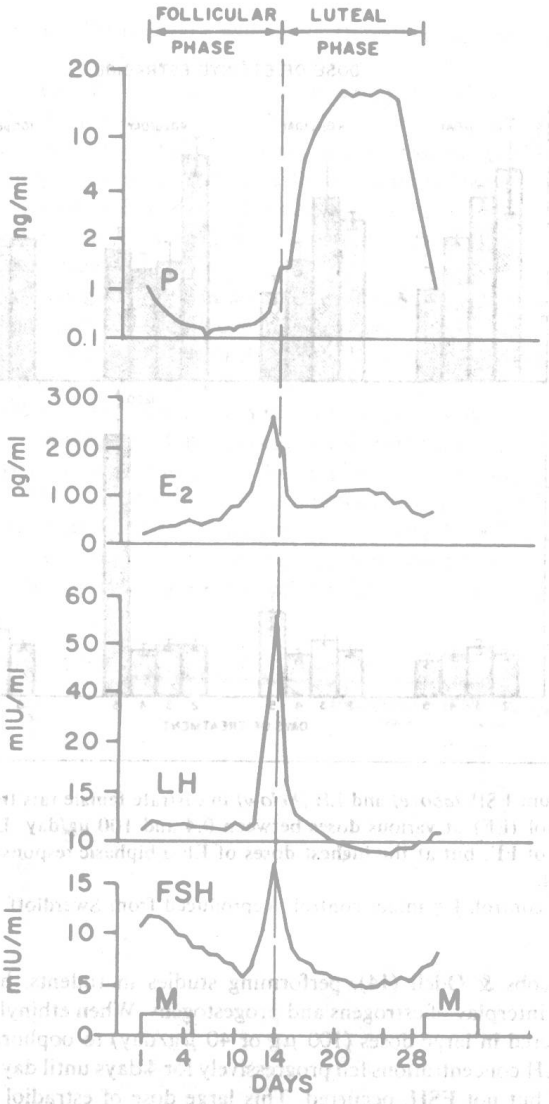

Figure 1 Schematized depiction of the fluctuations in progesterone (P), estradiol (E_2), luteinizing hormone (LH), and follicle stimulating hormone (FSH) during the normal menstrual cycle. Note that P in ng/ml (10^{-9} g/ml) is plotted on a log scale in order to show the small, but significant changes. Other abbreviations include pg/ml = picograms/ml (10^{-12} g/ml), mIU/ml = milliinternational units in terms of International Reference Preparation #2 of human menopausal gonadotropin. These data were modified from Abraham, Odell, Swerdloff & Hopper 1972 (6).

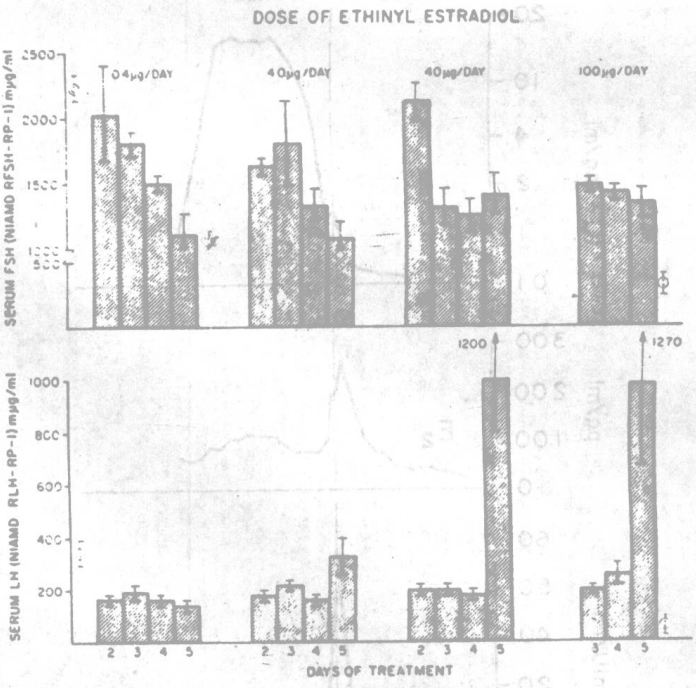

Figure 2a Serum FSH *(above)* and LH *(below)* in castrate female rats treated daily with ethinyl estradiol (EE) at various doses between 0.4 and 100 µg/day. LH and FSH fell with all doses of EE, but at the highest doses of EE a biphasic response in LH, but not FSH was noted.

C = castrate control, I = intact control. Reproduced from Swerdloff, Jacobs & Odell 1972 (14).

Swerdloff, Jacobs & Odell (14), performing studies in rodents, have assisted in clarifying the interplay of estrogens and progestogens. When ethinyl estradiol alone was administered in large doses (100 µg or 40 µg/day) to oophorectomized rats, the elevated LH concentrations fell progressively for 4 days until day 5 when a sharp surge in LH, but not FSH, occurred. This large dose of estradiol produced both negative and positive feedback. However, positive feedback was observed only for LH; no coincident FSH surge occurred. When lower doses of estradiol (4 µg or 0.4 µg/day) were administered, LH concentrations were suppressed, but no LH surge occurred on day 5 or any other day. Thus, under these conditions only negative feedback occurred. If, however, a single injection of progesterone or 20-hydroxy-pregnen-3-one[1] were given on day 5 in addition to the low dose of estradiol, a sharp

[1]This steroid is secreted in relatively large amounts by the rat. It does not appear to be of major importance in women. Conversely, 17-hydroxyprogesterone is secreted in large amounts in women, but did not increase LH or FSH in the studies in rats. Thus, different progestogens may be active in different species.

surge of LH and FSH occurred which exactly mimicked the ovulatory LH-FSH ovulatory surge in height and duration. These studies are illustrated in Figures 2a and 2b. One may thus hypothesize that estrogen secreted by the developing granulosal cells during the normal cycle is the prime ovarian signal determining the time of and triggering the LH ovulatory surge. Progesterone (or possibly other progestogens) appears to act as a fail-safe mechanism, lowering the threshold for estrogen stimulation of LH release. Progesterone (or another progestogen) appears to be necessary for the FSH surge that accompanies the LH ovulatory surge under normal circumstances.

Finally, the synergistic suppressive action of progestogens is important. Numerous studies show that estrogens alone in large doses suppress both FSH and LH but do not suppress them to undetectable concentrations (7–10). When FSH and LH are suppressed by estrogens to a maximal degree, the addition of large doses of a progestogen (if positive feedback does not occur) suppresses gonadotropins further. This phenomenon is observed during the normal menstrual cycle after the ovulatory surge; FSH and LH are lower during luteal phase than during follicular phase (4, 7, 8). FSH and LH concentrations rise toward the end of the luteal phase as estradiol and progesterone concentrations fall with functional corpus luteum death.

Therefore, like estrogens, progesterone (and in various species possibly other progestogens) acts in a complex way, both stimulating and inhibiting LH and FSH

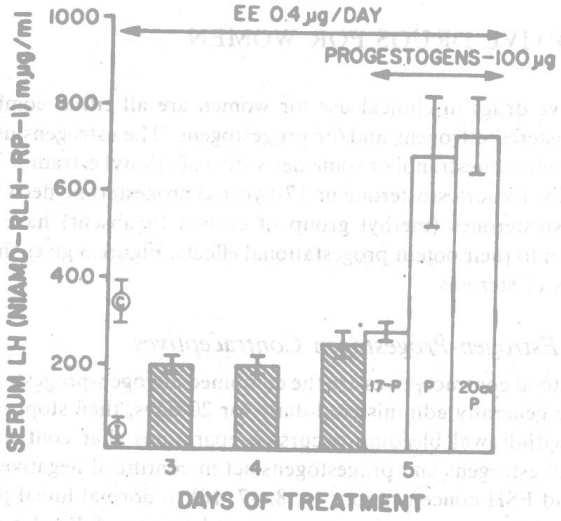

Figure 2b Serum LH after EE 0.4 µg/day plus either 17∝hydroxyprogesterone (17∝P), progesterone (P) or 20∝hydroxypregnen-3-one (20∝P). When a single dose of either P or 20∝P was added to the 0.4 µg of EE on morning of day #5, a surge of LH was observed; serum FSH was also increased.

From Swerdloff, Jacobs & Odell (14).

release. Sawyer & Everett (15) in 1959 first demonstrated this fact in rabbits. Because LH and FSH radioimmunoassays were not available, they used ovulation as an endpoint and demonstrated that ovulation in estrogen-primed rabbits was at first stimulated by progesterone and then inhibited. The explanation for this biphasic action of both progestogens and estrogens is unclear, but functionally it appears that once the positive stimulation or release of LH-FSH has occurred, then inhibition or negative feedback occurs and persists unless progestogens fall to low concentrations (or are discontinued).

In addition to their action as signals for the reproductive system, estrogens and progestogens of course have important other actions. Among their other effects are actions on the endometrium, cervix, and vagina in very specific ways to prepare for conception. Sperm entry through the cervical os is greatly affected by cervical mucous structure which is in turn modified by hormonal means (16). Once the sperm have entered the uterine cavity, migration to the fallopian tubes, the site of fertilization, is in major part hormonally controlled. After fertilization has occurred, the timing, migration of the fertilized ovum into the uterus, and implantation all require the orderly action of estrogens and progestogens. Contraceptive compounds, in addition to modifying the hormonal control of ovarian function, also may act on these later stages of fertility (i.e. sperm entry and postconception events up to and including implantation) (1).

CONTRACEPTIVE DRUGS FOR WOMEN

The contraceptive drugs in clinical use for women are all either combinations of or singly administered estrogens and/or progestogens. The estrogens used are usually potent synthetics, mestranol or some derivative of ethinyl estradiol. The progestogens are usually 19-nortestosterone or 17-hydroxyprogesterone derivatives. Most of the 19-nortestosterones (methyl group of carbon-19 absent) have androgenic effects in addition to their potent progestational effects. Figure 3 gives the structures of these families of steroids.

Combination Estrogen-Progestogen Contraceptives

The best understood contraceptives are the combined estrogen-progestogen preparations. These are generally administered daily for 20 days, then stopped for 5 days during which withdrawal bleeding occurs. Preparations that contain sufficiently large amounts of estrogens and progestogens act in continued negative feedback to suppress LH and FSH concentrations (7, 8, 17, 18) to normal luteal phase values. No LH-FSH ovulatory surge occurs to cause ovulation; no follicular phase rise in FSH exists to initiate follicle development. As a result of suppressed LH and FSH concentrations and the inhibition of follicle development, endogenous estradiol concentrations in blood also remain low (19). The early studies of Rock et al (20) and Garcia & Pincus (21), by directly observing the ovaries of women receiving these preparations, demonstrated that corpora lutea were absent and that developed

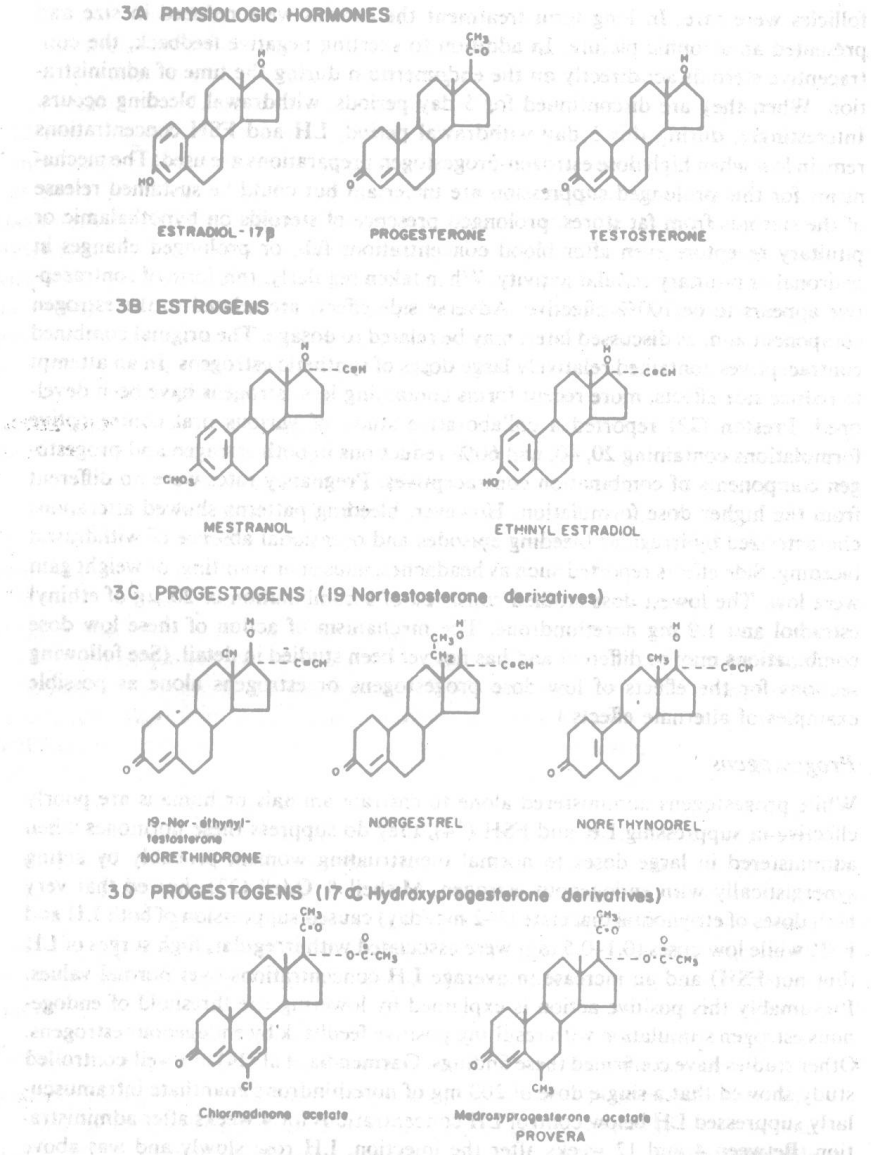

Figure 3 Structures of some steroids involved in the normal menstrual cycle and used as contraceptive agents.