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THE PHARMACOLOGY OF CONTRACEPTIVE AGENTS

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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.

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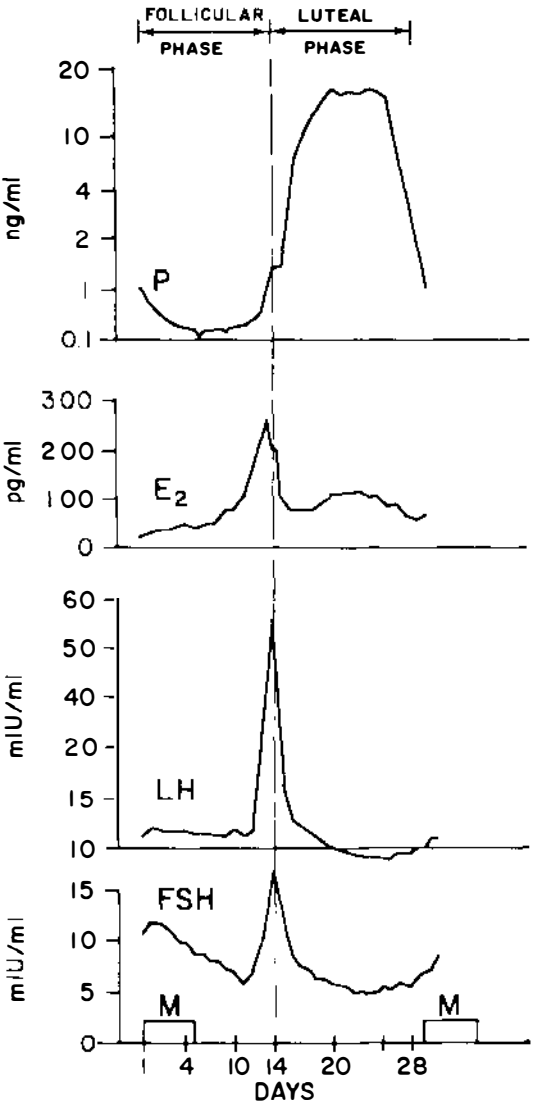

Figure 1 Schematized depiction of the fluctuations in progesterone (P), estradiol (E_2), luteinizing hormone (LH), and follicle stimulating hormone (FSH) during the normal menstrual cycle. Note that P in ng/ml (10^{-9} g/ml) is plotted on a log scale in order to show the small, but significant changes. 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).

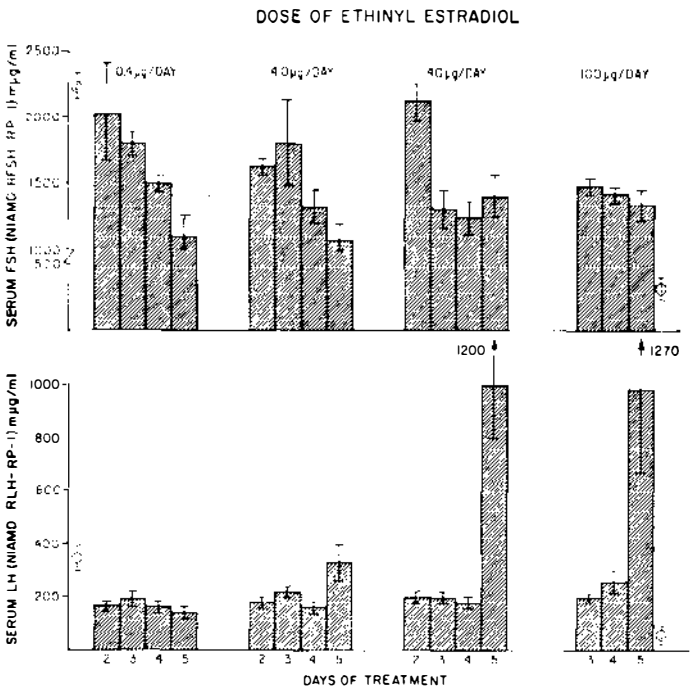

Figure 2a Serum FSH *(above)* and LH *(below)* in castrate female rats treated daily with ethinyl estradiol (EE) at various doses between 0.4 and 100 µg/day. LH and FSH fell with all doses of EE, but at the highest doses of EE a biphasic response in LH, but not FSH was noted.

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.

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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

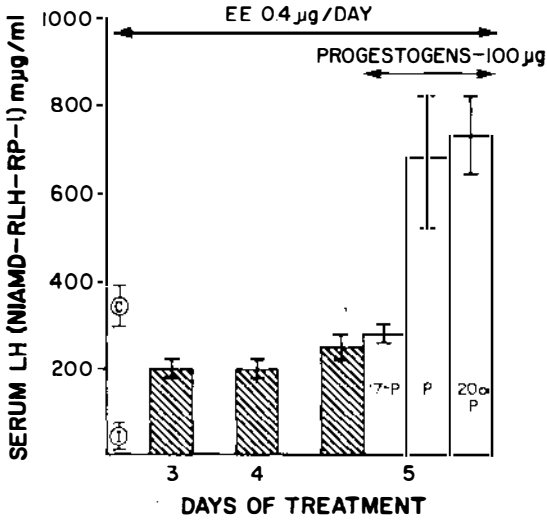

Figure 2b Serum LH after EE 0.4 µg/day plus either 17∝hydroxyprogesterone (17∝P), progesterone (P) or 20∝hydroxypregnen-3-one (20∝P). When a single dose of either P or 20∝P was added to the 0.4 µg of EE on morning of day #5, a surge of LH was observed; serum FSH was also increased.

From Swerdloff, Jacobs & Odell (14).

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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).

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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

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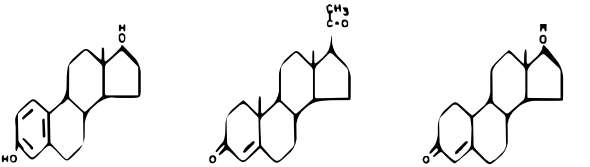
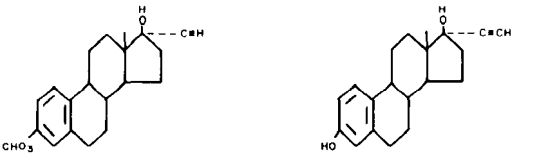
3A PHYSIOLOGIC HORMONES



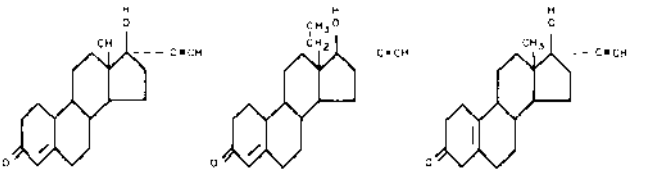
ESTRADIOL - 17β PROGESTERONE TESTOSTERONE

3B ESTROGENS



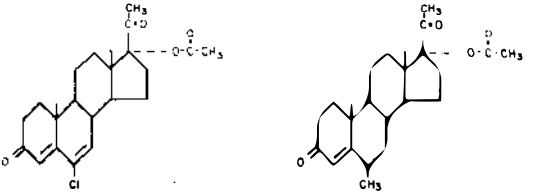
MESTRANOL ETHINYL ESTRADIOL

3C PROGESTOGENS (19 Nortestosterone derivatives)



19-Nor-ethynyl-testosterone
NORETHINDRONE NORGESTREL NORETHYNODREL

3D PROGESTOGENS (17αC Hydroxyprogesterone derivatives)



Chlormadinone acetate Medroxyprogesterone acetate
PROVERA

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

follicles were rare. In long term treatment the ovaries were reduced in size and presented an atrophic picture. In addition to exerting negative feedback, the contraceptive steroids act directly on the endometrium during the time of administration. When they are discontinued for 5 day periods, withdrawal bleeding occurs. Interestingly, during this 5 day withdrawal period, LH and FSH concentrations remain low when high dose estrogen-progestogen preparations are used. The mechanisms for this prolonged suppression are uncertain but could be sustained release of the steroids from fat stores, prolonged presence of steroids on hypothalamic or pituitary receptors even after blood concentrations fall, or prolonged changes in neuronal or pituitary cellular activity. When taken regularly, this form of contraceptive appears to be 100% effective. Adverse side effects are related to the estrogen component and, as discussed later, may be related to dosage. The original combined contraceptives contained relatively large doses of synthetic estrogens. In an attempt to reduce side effects, more recent forms containing less estrogens have been developed. Preston (22) reported a collaborative study of various oral contraceptive formulations containing 20, 40, and 60% reductions in both estrogen and progestogen components of combination contraceptives. Pregnancy rates were no different from the higher dose formulation. However, bleeding patterns showed alterations characterized by irregular bleeding episodes and occasional absence of withdrawal bleeding. Side effects reported such as headaches, nausea or vomiting, or weight gain were low. The lowest dose studied consisted of a combination of 20 μg of ethinyl estradiol and 1.0 mg norethindrone. The mechanism of action of these low dose combinations may be different and has not yet been studied in detail. (See following sections for the effects of low dose progestogens or estrogens alone as possible examples of alternate effects.)

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Progestogens

While progestogens administered alone to castrate animals or humans are poorly effective in suppressing LH and FSH (14), they do suppress these hormones when administered in large doses to normal menstruating women, probably by acting synergistically with endogenous estrogen. Mishell & Odell (23) showed that very high doses of ethynodiol diacetate (1–2 mg/day) caused suppression of both LH and FSH while low doses (0.1–0.5 mg) were associated with irregular, high surges of LH (but not FSH) and an increase in average LH concentrations over normal values. Presumably this positive action is explained by lowering the threshold of endogenous estrogen stimulation with resulting positive feedback by endogenous estrogens. Other studies have confirmed these findings. Garmendia et al (24) in a well-controlled study showed that a single dose of 200 mg of norethindrone enanthate intramuscularly suppressed LH below control LH concentrations for 4 weeks after administration. Between 4 and 12 weeks after the injection, LH rose slowly and was above control concentrations by the 12th week. A second group of women received a low dose (0.03 mg orally/day) of *d*-norgestrel; irregular LH surges were observed and mean LH concentrations were higher than normal. Moghissi et al (25) showed that 359 μg/day of norethindrone inhibited both the FSH rise initiating follicle growth

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and the midcycle LH ovulatory surge. These changes alone would explain contraceptive actions. Foss et al (26) showed that the minimum contraceptive dose of *dl*-norgestrel was 50 μg/day. Rudel (27), quoting unpublished studies of Martinez-Manatou, stated that contraceptive effectiveness of chlormadinone acetate was directly related to the dosage between 0.1 and 0.5 mg/day, with megestrol between 0.25 and 5 mg/day and norethindrone between 0.05 and 0.5 mg/day. With sufficiently small doses of any of these progestogens, a normal secretory endometrium was observed. As the dosage was increased, there was progressive reduction in glandular secretion and tortuosity. Martinez-Manautou et al (28), Foss et al (26), and Wright et al (29) have shown that very low dose progestogen treatment is associated with ovulation in many cycles, indicating the hormonal mechanisms described for the normal cycle are still likely to be occurring in some cycles. If ovulation is common, mechanisms other than those discussed would appear to be of major importance, at least for some dosages of progestogen contraceptive. Moghissi et al (25) showed that properties of cervical mucous (spinnbarkeit and ferning) were altered with low dose progestogen. Probably as a result, sperm penetration into the uterine cavity was also abolished. Vaginal sperm number and motility were similar to nontreated controls postcoitally; uterine sperm were absent in the treated group and present in large numbers in the nontreated group. Roland (30) had shown previously that sperm migration into the uterine cavity was inhibited by microdose progestogens.

In summary, the mechanisms of action of progestogens administered alone are complex and relate to dosage. High doses suppress LH and FSH with inhibition of follicular development but also commonly inducing aberrant LH surges not timed to coincide with any follicular development. Still lower doses may be associated with normal follicular development and ovulation but also act as higher doses do by modifying cervical mucous composition and preventing sperm entry into the uterine cavity. Lastly, endometrial histology is altered which may interfere with implantation should fertilization occur.

Progesterone treatment, while effective as a contraceptive, is often not associated with regular menses; bleeding is irregular and unpredictable. High dose progestogen treatment is also associated with intermittent or unpredictable vaginal bleeding. In addition, high dose depo progestogen treatment may be associated with prolonged periods of amenorrhea. Because of these effects and the associated infertility, high dose depo injections of progestogens are not usually recommended for nulliparous women.

Estrogens

Low dose estrogens also decrease fertility when administered cyclically for 20 days, followed by discontinuation for 5 days. Estrogens administered alone to normal women act in positive feedback to stimulate LH surges in bizarre, unpredictable fashion, similar to the pattern observed following progestogens alone (18).

Recently, a once-a-month estrogen pill has received clinical trials and has been shown to be an effective contraceptive (31–36). Quinestrol (an estrogen) is stored

in body fat and subsequently is released slowly and probably converted into ethinyl estradiol. Quingestanol acetate (a progestogen) is the 3-cyclopentylenol ether derivative of norethindrone acetate. Quingestanol is a short acting progestogen. Thus, when a combination pill of quinestrol and quingestanol is taken once each 4 weeks, menses usually occur 3–4 days after the pill because of the rapid falloff in progestational effects on the endometrium. The estrogen produces the contraceptive effect and is effective for prolonged periods due to its peculiar fat-soluble properties. Nudemberg et al (35) showed that this contraceptive abolished ovulation; FSH concentrations were quite constant during treatment and no follicular phase rise or midcycle FSH surges were observed. LH was variable, some patients were observed to have double surges to heights comparable to those causing ovulation in normal subjects. These actions, of course, are predictable from the effects of steroids discussed previously for control of the normal cycle. In animal and human studies, estrogens usually suppress FSH, and at times LH, but also may stimulate LH secretion due to positive feedback. As indicated, progesterone measurements were not consistent with ovulation. This contraceptive might also act by abolishing the FSH-induced follicular development.

Sequential Estrogen Plus Progestogen Preparations

These preparations consist of an estrogen administered alone for a number of days (usually 15) followed by estrogen plus progestogen for several days (usually 5). The drugs are discontinued for 5 days to permit withdrawal bleeding, and the sequence is repeated. The effects of these preparations, predictably, are suppression of FSH with a stimulation of erratic LH surges during the estrogen only phase, usually a stimulation of another LH surge at the onset of the progestogen, followed by a suppression of both LH and FSH as the combination is continued (18).

Postcoital Contraceptives

Estrogens administered in large doses are currently being used as postcoital contraceptives for large numbers of patients, particularly on college campuses. In large doses these substances greatly shorten transit time of the fertilized ova into the uterine cavity (36). In both the rat and mouse, the amount of estradiol required to prevent nidation is 50 to 100 times greater than that required to initiate nidation. Thus, the dose required for contraception postcoitally in humans is also large, usually 15 mg of diethylstilbestrol daily for several days (37, 38).

Recently, Kesseru et al (39) reported that a single dose of *d*-norgestrel (a progestogen) taken within 3 hr of sexual intercourse could prevent pregnancy. Doses of 150 to 400 μg were studied. The contraceptive action was poor with 150 and 200 μg doses but was excellent with the 400 μg dose. In 2801 patients receiving this dose for an average of 9.1 months and averaging 8 coital exposures per month, the corrected failure rate was 1.7. The only side effects noted were cycle disturbances, most often a shortening of cycles. One third had intervals between bleedings of less than 20 days. Fewer than 10% of the patients had any complaints other than cycle length disturbances. Discontinuation rate of the drug was lower than that observed for oral microdose or long acting parenteral methods.

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Steroid Administration from Silastic Preparations

In 1964 Folkman & Long (40) demonstrated that physiologically active materials would diffuse through the wall of a silicone rubber capsule at a steady, sustained rate. Dziuk & Cook (41) reported that silicone implants into ewes would allow sustained and constant steroid administration. This technique has now been applied to administer progestogens at low constant doses to women. Segal & Croxatto (42) further documented the findings of Folkman & Long (40) and added that dosage of the steroid could be adjusted by varying the surface area and wall thickness of the capsule. Croxatto et al (43) implanted subcutaneous capsules in women and demonstrated effective contraception using low dose progestogens as the steroid. Tatum et al (44) also performed such a study. They showed that contraception effectiveness was directly related to the number of capsules implanted and thus to steroid dosage administered. These findings were similar to those reported by Martinez-Manautou (28) using oral progestogens. There were no local or systemic complications attributable to the implants in the 24 women studied by Tatum et al. Mishell et al (45) have recently reported the use of silicone rings (55 or 65 mm outside diameter) impregnated with progesterone which were inserted intravaginally on day 5 of the cycle in 24 women and left in place 3 weeks. Absorption was sufficient to inhibit ovulation. The only complication, observed in a few patients, was superficial vaginal ulceration which healed quickly and spontaneously. The smaller devices were not associated with such ulceration. There was less breakthrough bleeding than when such steroids were given orally. The concept of using silastic impregnated devices is attractive, since theoretically the steroids released could supply constant dosage for years. In addition, absorption through mucous and dermal membranes makes a variety of potential devices possible.

Intrauterine Devices

Intrauterine devices (IUDs) have been increasingly used as antifertility agents, especially in underdeveloped countries, because of low cost, high efficiency (96%), minimal side effects, and no necessity for daily pilltaking, physician attention, or laboratory follow-up. The IUDs are of three types: 1. the older, purely mechanical devices made of steel or polyethylene and barium sulfate mixtures, 2. The newer copper and zinc devices, and 3. the still experimental steroidal releasing IUDs.

The earlier mechanical devices consisted of various types of rings (Hall), bows (Birnberg), and loops (Margulies spiral, Lippes loop) which were associated with the side effects of abnormal uterine bleeding, cramping, and expulsion from forcing the uterine cavity to adjust to the size and shape of the IUD (46). Although the efficacy was 98–99%, the rate of discontinuance of these IUDs was 23% after 1 year and 35% after 2 years of use because of these side effects (46). More recent IUDs include a T-shaped device (in which the arms of the T extend into the cornua) with a low rate of side effects but an 18% pregancy rate, and the Dalkon shield, a small pear-shaped device covered with a plastic membrane, giving a large surface area. In two studies (47, 48) this latter device has been found to have a pregnancy rate of 1 and 2.4% and removal rate of 4.9 and 14.5% after 1 year of use, yielding a net retention rate of 94% at 1 year.

The mechanism of the antifertility action of these IUDs remains unclear. Normal ovulatory cycles do occur (49). The IUDs all induce a sterile inflammatory reaction in the endometrium with a polymorphonuclear outpouring into the intrauterine cavity. These leukocytes may contain a toxic substance that affects implantation of fertilized ova rather than sperm viability and motility. Other possible mechanisms include the acceleration of ova transport through the fallopian tube and the increase in endometrial development, causing an environment inhospitable to implantation (1, 49).

Copper wire-bearing IUDs have been in use since 1967 and the efficiency of pregnancy prevention is directly proportional to the surface area of the copper wire on the IUD (46). The pregnancy rate of the most current models (using approximately 200 mm^2 of surface area) is 0.8% using the T-shaped device (50) and 1.1% using a number 7-shaped device (51), with an overall IUD retention rate at one year of 79% for the T and 76.8% for the 7 (50,51). Other devices using zinc in addition to copper are also being tested, and preliminary reports show even greater effectiveness (52).

The copper in these IUDs causes an increased copper concentration in the secretory endometrium, in endometrial fluid, and in cervical mucous, but not in plasma. A gradual decrease of 7 to 26 mg of the copper content of the IUD occurs each year (46, 53, 54). A polymorphonuclear leukocyte outpouring similar to the inert IUDs is also seen (55). The presence of copper (and to a less extent, zinc and silver) in cervical mucous is inhibitory to sperm migration in humans and animals in vitro (56, 57). In addition, in vitro experiments have shown a toxic effect of cupric chloride on mouse blastocysts (58).

The most recent innovation in IUDs has been the steroidal releasing devices. Preliminary animal work has shown progestogens are slowly released locally from silicone elastomer IUDs, and significant contraceptive action was found (56). Clinical trials (59) using a T-shaped IUD that released 50 μg/day of progesterone showed a pregnancy rate of 1.4%, an overall expulsion rate of 2.3%, and a removal rate of 8.1%. The progesterone apparently induces the production of decidua that blocks implantation. It appears that this IUD will require periodic changing, however, to renew the hormone supply.

ORAL CONTRACEPTIVES—METABOLIC AND SYSTEMIC EFFECTS

The combination estrogen and progestogen and progestogen-only oral contraceptives (OC) currently available have been associated with many metabolic changes and adverse systemic effects, many of which have been reviewed elsewhere (60–64). In this next section we will attempt to review the most recent findings in this area (See Table 1).

Thromboembolic Phenomena

The retrospective studies of the British Research Council were the first to demonstrate an increased risk of thromoembolic phenomena in OC users; the risk was

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Table 1 Systemic effects of combined estrogen-progestogen oral contraceptives

Venous thromboembolism	Depression
Cerebrovascular accidents	Nausea
Hypercoagulable state	Vomiting
Defective folate metabolism	Abdominal cramps
Altered hepatic protein synthesis	Dizziness
Abnormal glucose tolerance	Edema
Hyperlipidemia	Breast soreness
Hypertension	Backache
Defective lactation	Fatigue
Post-use amenorrhea	Increased appetite
Hepatic dysfunction	Weight gain
Melasma	Nervousness
Erythema nodosum	Leg cramps
Gall bladder disease	Photosensitivity

directly correlated with the dose of estrogen in the preparations (65–68). Similar findings have been reported in American (69, 70) and Swedish (71) studies. An association has also been described for intracranial venous thrombosis (72). Prospective studies, however, have not borne out the association between OC use and thromboembolism (73). Drill, in 1972, reviewed (74) several large-scale prospective studies and found "an average figure of 0.92 cases per 1000 women per year of thromboembolic disease which he compared with a figure of 2.2 cases in women not on OC. However, this latter number was derived from several different studies and is thus also open to question. The conclusions reached in these analyses of prospective and retrospective studies are at marked variance and are difficult to explain. It would seem that an internally controlled, double-blind large prospective study of this problem is warranted.

Two mechanisms have been proposed for the controversial increased incidence of thromboembolism in women taking OC: 1. an increased tendency toward clotting (see below) and 2. venous stasis. A decrease in the elasticity and tone of the smooth muscle of the peripheral vascular system due to OC estrogens has been hypothesized as one of the causes of decreased flow and stasis (75).

Although the incidence of headache was not increased in women on OC, those reporting headaches often experienced significant relief when stopping OC (76). However, there is evidence for a definite association between cerebrovascular disease and OC use; about 25% of the patients having an occlusion suffered from an occlusion in the vertebrobasilar distribution (78). Recently, an extensive, collaborative, retrospective study was published (79) from 12 medical centers in the United States. Each subject with cerebrovascular disease had an age and race matched

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control from the hospital population and a second, healthy, similar control from the same neighborhood. This study showed that the risk of a thrombotic stroke was 9.5 times greater from combined OC users than for hospital controls and 8.8 times greater than for neighbor controls. The relative risk for hemorrhagic stroke was 2.0 for OC users vs hospital controls and 2.3 vs neighbor controls, with no increased risk for other types of stroke.

Other associations with vascular complications have been suggested but have been less well documented. For example, Inman and Vessey (77) found a slight increase in OC use in patients dying of coronary artery disease but this was not statistically significant. Mesenteric arterial insufficiency has also been reported in women on OC (80).

Progestogen-only OC have so far not been associated with increased risk of vascular disease (81–85). However, in the combined preparations, Inman et al (67) found that the progestogen (megestrol) was associated with venous thromboembolic disease but not cerebral or coronary disease.

Hematologic Changes

Combination OC have been reported to affect the coagulation process in several ways. Clotting factors II, VII, and X are elevated (86, 87) as is plasminogen (88), but fibrinogen has been reported as either elevated (88) or unchanged (87). Antithrombin III and antiplasmin have been found to be low (88, 89). Although there is a decrease in fibrinolytic inhibitor, there is normal fibrinolytic activity on combined OC (90). Clots formed in women on combined OC are also significantly more stable than in controls (91). The net effect of these changes is uncertain. Although some have suggested the existence of a "hypercoagulative state," present testing systems are inadequate to prove or disprove this. Progestogen-alone OC have been found to cause either no change in these parameters (88) or to decrease antithrombin III (92), increase factors VIII and IX and decrease V (93), and decrease fibrinolytic activity (90).

Platelet studies have yielded conflicting results. Although significant increases in platelet aggregation have been found (86, 94), no increases have been found in platelet adhesiveness (95). An increase in aggregation has also been found with progestogen-only OC, though not so marked as in the combined preparations (96).

Oski et al (97) have shown a decrease in RBC filterability within 3 days of onset of OC. These authors suggest a decrease in RBC deformability, with perhaps a tendency for these cells to be trapped in the microcirculation leading to stasis.

Although no changes in hemoglobin level (98) or platelet counts (95) have been found, women on combined OC have an absolute increase in neutrophil count and a smaller increase in lymphocyte count (99). Serum folic acid levels have been found to fall with time in women on OC in some studies (100) but not others (101) without a change in hemoglobin levels (100). The low folate has been attributed to defective absorption of dietary folate, the folate polyglutamates (102), or to an increased clearance of folate from plasma to tissues (101).

Combined OC have been found to increase serum transferrin, total iron binding capacity (TIBC), and iron (103–106) with the rise in TIBC and iron independent of each other (104). Increased synthesis by the liver is thought to cause the rise in

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transferrin, but the mechanism for the increased serum iron is unknown because iron absorption is normal (105). Progestogen-only OC have been reported to both increase (107) and not change (108) serum iron and TIBC levels.

Other hepatically synthesized proteins elevated by combined OC include α-1-globulins (109), α-2-macroglobulins, IgG (110), IgM, ceruloplasmin, α-1-antitrypsin (111), cryofibrinogens (112), tyrosine aminotransferase (113), α-amylase (114), Vitamin B_{12} binding capacity, thyroxine binding globulin (TBG), and cortisol binding globulin (CBG) (115). Albumin decreases in women on OC (111). Other circulating substances increased by OC include Vitamin A (116), copper (117, 118), phosphorus, and calcium (119), with no change in magnesium (119) and a decrease in zinc (117) and the amino acids proline, glycine, alanine, valine, leucine, tyrosine, glutamate, and isoleucine (120). Combined OC have induced positive lupus erythematosus cell preparations in some series but not in others (121).

The elevated TBG concentrations result in elevated total thyroxine and triiodothyronine concentrations, but the concentrations of the free hormones remain normal (122). In addition, increases in plasma cortisol result from the increased CBG and increased testosterone from the increased sex hormone binding globulin (124, 125). While the hypothalamic-pituitary axis has been reported to be normal (124), the single dose 1 mg dexamethasone suppression test is frequently abnormal because cortisol concentrations commonly remain above 1 μg% (due to increased CBG). Surprisingly, increased free cortisol in plasma and decreased urinary excretion in 17-hydroxy and 17-ketosteroids have been reported; these findings, if true, can not be explained by increases in cortisol binding globulin alone (124, 125). Contraceptives containing only progestogens do not increase TBG (123) or CBG and sex hormone binding globulin (125).

Glucose Tolerance

Combined OC have been found to induce a mild to moderate deterioration of glucose tolerance in many women (126–129). In addition, distinct worsening of the GTT (Glucose Tolerance Test) was correlated with previous gestationally abnormal GTT curves (130). Progestogen-only OC were not found to cause abnormal GTTs in most studies (131–135), but Vermeulen et al (135) found increased insulin values in some patients despite normal GTTs. This deterioration of glucose tolerance has also been found frequently in postmenopausal women treated with estrogens (136). Administering OC to panhypopituitary women in addition to their usual thyroid and cortisol replacement, Davidson & Holzman (137) found no evidence of insulin resistance on tolbutamide tolerance testing when compared to controls on OC, suggesting that growth hormone might be the cause of the deterioration of glucose tolerance in normal women on OC. The normals had exaggerated growth hormone responses to tolbutamide while the hypopituitary patients, of course, had no response.

Lipid Metabolism

Serum triglycerides have been found to be elevated in 60 to 96% of women taking combined OC (126, 138, 139), with an average rise of 33 mg/100 ml (139). These elevations are associated with increases in low density lipoproteins (LDL) and very

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low density lipoproteins (VLDL) (139). The elevations slowly return toward normal over several weeks when a progestogen-only OC is substituted for the combination (140), and a dose-response relationship between the dose of estrogen in the OC and the level of triglycerides has been found (141).

The mechanism for the rise in triglycerides is unclear. Post-heparin lipolytic activity (PHLA) is decreased in women on combined OC, but there is no actual defect in triglyceride removal from serum (142). Kekki & Nikkila (143) have demonstrated an increased triglyceride synthesis by the liver in women on OC.

Cholesterol has generally been found to be either unchanged or slightly elevated in women on combined OC (139, 144, 145). Occasionally very large increases in triglycerides and cholesterol have been found, usually in patients with an underlying hyperlipidemia (146–149). No changes in serum triglycerides or cholesterol have been demonstrated in patients on progestogen-only OC (132).

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Hypertension

Both prospective (150–152) and retrospective (153–154) studies have generally agreed on a definite association between combined OC use and the development of hypertension in some women, although there are some dissenters (155, 156). The incidence figures range from 1% (151) to 15.41% (150); the former figure is in fact less than the 2% of the normal population expected to develop hypertension in the 25–34 year age group (157).

Studies of the renin-angiotensin-aldosterone system have shown increased renin substrate (158), plasma renin activity (158), angiotensin II (159), and aldosterone (160) in all women on combined OC. However, only some of these women develop hypertension, reflecting some additional genetic or environmental factor necessary to cause hypertension in certain individuals. Progestogen-only OC have as yet not been implicated in the development of hypertension.

Lactation

Reports of combined OC effects on postpartum lactation have been conflicting, with some investigators reporting increased milk production and baby weight (161) and others finding decreased milk production and baby weight gain (162–164) and decreased milk protein and fat content (165). In addition to the effects of OC on milk production, a significant correlation has been found between prior OC use and breast milk-related jaundice in the infant, due to estrogen interference with bilirubin conjugation by an unknown mechanism in the neonate (166).

Amenorrhea

A small percent of women taking combined OC develop prolonged amenorrhea upon discontinuation of medication. Although good incidence figures are lacking, Shearman (167) estimated that only 1% of women will develop amenorrhea persisting for more than 12 months. A few of the patients have elevated gonadotropin and premature menopause, but most have normal or low serum and urinary gonadotropins and urinary 17-ketosteroids when measured. In some series, over 50% of the women developing this syndrome had considerable menstrual irregularity before

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going on OC and a few of these proved to have the polycystic ovary syndrome. Clomiphene citrate with and without additional human chorionic gonadotropin (HCG) treatment has induced ovulatory cycles in 50–75% of these women with smaller proportions of these resuming normal ovulatory cycles or becoming pregnant. Interestingly 10–20% of women with this syndrome have galactorrhea with normal skull roentgenograms (167–171). As yet no studies have been done on large numbers of these patients utilizing daily serum LH, FSH, estrogen, and prolactin levels, although Frantz (190) has reported elevated prolactin levels in six of these patients. However, the data would seem to indicate that most of these patients have normal gonadotropins but probably fail to have an ovulatory surge of LH either because of a lack of the estrogen rise prior to the LH surge or because of a lack of response on the part of the hypothalamus to such a rise if it occurs. The significant percentage of such patients with galactorrhea and the response of many to clomiphene citrate implicate hypothalamic dysfunction as the possible etiology. Experience with low dose progestogen-only OC is too short to determine whether amenorrhea will be a problem with their use.

Depression

Anecdotal reports of depression associated with the use of combined OC, especially in women prone to premenstrual tension, have been found in the literature. However, large surveys (172, 173) and two double-blind studies using placebo controls (174, 175) have failed to confirm these reports. A preliminary report by Baumblatt & Winston (176) of 58 women with OC-related depression states that supplemental pyridoxine was able to reverse this depression in 44 (76%). Adams et al (191) have had similar results. The estrogenic component of OC increases pyridoxine utilization by inducing an increase in the enzyme tryptophan oxygenase and a general increase in tryptophan catabolism via pathways that use pyridoxine (177). This increased activity makes less pyridoxine available for the decarboxylation of 5-hydroxytryptophan to serotonin. Since low serotonin levels have been found in some depressed patients, according to these authors, supplemental pyridoxine would increase serotonin and reduce depression in some women on OC. Progestogen-only OC have not been associated with depression (84).

Hepatic Dysfunction

Combined OC have been associated with BSP retention in about 20% of patients, rises in alkaline phosphatase in 2%, and elevations of transaminases in up to 18%, but these elevations are usually transient and have not been regarded as necessitating discontinuance of the drug (62, 64). Cholestatic jaundice has also been reported in isolated cases (62). Recent investigations of giving OC to women with recently resolved viral hepatitis (178), obstructive jaundice (179), and previous jaundice of pregnancy (179) have not shown any deleterious effects, although serum transaminases did go up transiently after 3 weeks of use. Most authors would agree that liver function testing should be more frequent than usual in women with a prior history of liver disease. Although most investigators seem to accept slight elevations of BSP and continue with OC use (64), O'Malley et al (180) have shown impairment of

antipyrine and phenylbutazone metabolism (the latter drug not statistically significant) in women on OC; both drugs are metabolized principally by the liver. More drugs should be studied with regard to this potentially widespread area of drug-drug interaction in which OC-induced liver changes might alter the metabolic degradation rates of various drugs.

Skin

Melasma is the most common skin complication and occurs in 5–8% of women on OC within 1–20 months of the start of therapy. Either component of the combined OC can cause an increase in pigmentation, but the combination brings it on more frequently. It appears that the estrogens stimulate melanocytes and the progestogens cause the pigmentation to spread. Sunlight worsens the condition. The pigmentation usually fades slowly after OC use is discontinued, but it may be permanent. Acne is usually improved due to the estrogenic component, although there may be a paradoxical worsening of the acne in the first few months of therapy. Vaginal moniliasis is more common in patients on OC as well as photosensitivity, erythema nodosum, telangiectasias, and spider nevi (181).

Miscellaneous Changes

OC use has not to date been associated with any breast disease. The incidence of OC use among patients with benign and malignant breast tumors was not increased in two separate studies (70, 182). Similarly, OC use has not been related to opthalmological abnormalities when compared to controls (183). On the other hand, surgically proven cholecystitis and cholelithiasis have been found slightly but significantly more frequently in OC users (70).

In cytogenetic studies some investigators have found significantly increased chromosome breakage and satellite association (184), but others have been unable to find such breaks or increases in mitotic indices (185, 186).

In addition to the above serious and sometimes irreversible side effects, there are many other symptomatic side effects of a more general nature that can be of such intensity and discomfort as to cause many patients to stop using OC. These effects include nausea, vomiting, abdominal cramps, dizziness, nervousness, edema, breast soreness, leg cramps, backache, fatigue, increased appetite, and weight gain. Many of these can be related on a dose basis to the estrogenic component of combined OC (22). Progestogen-only OC seem to be free of most of the above side effects, with most problems in patient acceptance being the abnormal bleeding (81, 82) and occasionally amenorrhea (187).

All of the above side effects condition the rate of patient acceptance and the reliability of use. In one 4 year prospective study of over 2000 women, the overall continuation rate for combined OC was 81% at 1 year and 50% at 4 years; the rates for sequential OC were 83% at 1 year and 36% at 1 year. The reasons for discontinuation included accidental pregnancy, planning future pregnancy, and personal reasons, with medical reasons being 13.1% of the total at 4 years with combined OC and 20.7% for sequential OC (188). A similar recent study by Hall (189) showed a 28% discontinuance of sequential OC at 2 years for medical reasons. With the

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progestogen-alone OC, abnormal bleeding caused most of the medical reasons for discontinuing the OC, with rates of 8% for continuous use (81) and 11.6% for cyclic use (30). Pregnancy rates for combined OC were 0.9% for 1 year and 2.1% cumulatively after 4 years (188), for sequential OC 2.0% at 1 year and 4.3% at 4 years cumulatively (188), and for continuous progestogen-only OC 4.5% per year (81).

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