Manipulation of the menstrual cycle

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The physiological mechanisms involved in controlling the ovarian and menstrual cycles are reviewed. With the exception of the combined contraceptive pill, widespread application of the existing methods of contraception in women is limited by their effects on the pattern of menstruation as well as by their effectiveness. Many attempts to manipulate the ovarian cycle for contraceptive purposes have unacceptable effects on the menstrual cycle. The possibility of producing amenorrhoea by altering the level of hypothalamic activity to mimic the state existing prepubertally and during lactation is discussed.

Introduction

Menstruation is the obvious manifestation of the secretory activity of the ovaries. It is defined as periodic bleeding from the uterus due to withdrawal of hormone support from the endometrium (Corner 1951). True menstruation appears to be confined to man and those species of Old World primates in which the endometrium is supplied by specialized spiral arterioles, although tiny amounts of blood may be lost from the uterus in the absence of spiral arterioles.

Although the hormonal basis of menstruation has been established for many years (Heape 1897; Markee 1940; Corner 1951), recently there have been considerable advances in our understanding of the relation between the hypothalamic-hypophyseal system and the ovaries. To date any alteration in menstrual pattern has usually been secondary to attempts to manipulate the ovarian cycle for contraceptive purposes. These alterations in menstrual pattern may be of therapeutic benefit by alleviating the morbidity associated with menses, for example when the combined oestrogen-gestagen pill is used to treat dysmenorrhoea or menorrhagia (Klopper 1970). On the other hand the widespread acceptance of a contraceptive may be limited because of irregular menstrual bleeding as with the low dose gestagen pill. Thus the usefulness of any contraceptive technique will depend not only on its effectiveness in preventing pregnancy but also on the absence of unacceptable side effects of menstruation.

This paper will summarize current concepts of the hormonal control of menstruation and the ovarian cycle and indicate where current contraceptive technology interferes with these physiological mechanisms.
Ovarian cycle

Follicular growth is probably a continuous process which begins in foetal life and ends at the menopause (Peters, Byskov, Himelstein-Braw & Faber 1975). The number of primordial follicles recruited for further development is independent of gonadotrophins but is related to the total number of small follicles in the ovary. Gonadotrophins are necessary for the continued growth of medium and large follicles the rate of atresia of which is related to the level of gonadotrophins.

In the mouse the time taken for a primordial follicle to develop into a pre-ovulatory Graafian follicle is about 26 days (Pedersen 1970). In women it is unlikely that the phase of the follicular cycle which is dependent on gonadotrophin exceeds 8–10 days because ovulation can be induced in less than this time by the administration of exogenous gonadotrophins in hypogonadal women (Gemzell 1965). The length of the follicular phase in women (10–14 days) probably represents the time necessary to develop a primary or small antral follicle to the point of ovulation. The development of small antral follicles (diameter < 1 mm) depends on a carefully coordinated sequence of events which results in the formation of a pre-ovulatory follicle, ovulation and subsequently a corpus luteum. As the corpus luteum of the previous cycle regresses the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) rise and FSH enters the lumen of some small antral follicles (McNatty, Hunter, McNeilly & Sawers 1975). Under the influence of this gonadotrophin the granulosa and theca cells proliferate and the follicle synthesizes increasing amounts of oestradiol. The elevated levels of oestradiol in blood inhibit secretion of FSH from the pituitary and hence the majority of developing follicles become atretic. The follicle destined to ovulate, however, is probably protected from atresia by the fact that the high concentration of oestradiol within the follicle makes it increasingly sensitive to gonadotrophins (Bradbury 1961; Goldenberg, Vaitukaitus & Ross 1972). FSH (and probably oestradiol) have been shown to increase the number of receptors for LH on the surface of granulosa cells (Channing & Kammerman 1974).

When the pre-ovulatory follicle is mature it secretes sufficient oestradiol to induce a discharge of LH (positive feedback) which results in ovulation some 24–36 h later (Yussman & Taymor 1970; Baird 1974). If this pre-ovulatory surge of LH fails to occur or if the timing is not synchronized with the development of the follicle and oocyte, then an abnormal cycle (anovulatory or defective luteal phase) will result.

Although it is known that the pre-ovulatory discharge of LH is necessary for ovulation, the mechanism of follicle rupture is unknown (Rondell 1974). In rats and rabbits there is a marked rise in the concentration of prostaglandins E2 and F2α (PGE2; PGF2α) in follicular fluid within a few hours of the LH surge (Tsairiri, Lindner, Zor & Lamprecht 1972). This rise in prostaglandin appears to be important in the process of rupture of the follicle because if it is prevented by administration of antibodies to prostaglandins or by inhibitors of prostaglandin synthesis (e.g.
indomethacin) ovulation does not occur (O'Grady, Caldwell, Buletta & Speroff 1972). The resulting 'luteinized follicle' containing the oocyte trapped within it, apparently functions in a manner similar to the corpus luteum.

The corpus luteum which in women is formed by both theca lutein as well as granulosa lutein cells, secretes oestradiol and progesterone (Baird, Baker, McNatty & Neal 1975) which inhibit the release of FSH and LH so that they reach their lowest levels in the mid to late luteal phase of the cycle (Ross & Vande Wiele 1974). LH and possibly prolactin are required for the normal functioning of the corpus luteum. During the pre-ovulatory surge of LH the receptors in the granulosa cells probably become fully saturated (Lee, Conlam, Jiang & Ryan 1973). In the luteal phase uptake of further LH from blood by the corpus luteum will be aided by an increasing number of free receptors as the LH gradually dissociates over the few days following ovulation. Unless the granulosa cells are properly programmed by the correct sequence of gonadotrophins during the follicular phase, normal luteal function does not occur (McNatty et al. 1975). Thus the so-called defective or short luteal phase is frequently associated with abnormalities in the secretion of FSH in the follicular phase of the cycle (Ross et al. 1970).

Unless pregnancy occurs, the corpus luteum undergoes degenerative changes and regresses some 10 days after ovulation. In the pregnant cycle, human chorionic gonadotrophin (HCG) can be detected in serum at about the time of implantation (7 days after ovulation) (Wide 1969) and it is likely that the exponential rise in the secretion of HCG from the cytotrophoblast is responsible for the maintenance of the corpus luteum of pregnancy. Injections of exogenous HCG stimulate the secretion of progesterone by the corpus luteum (Hanson, Powell & Stevens 1970) and can extend its life span for up to 2 weeks beyond the expected date of menstruation (Bradbury, Brown & Grey 1950).

The cause of luteal regression in the non-pregnant cycle is unknown although it is not due to the production of a uterine luteolytic factor as in many lower mammals. Luteal regression occurs normally in women in whom the uterus is absent either congenitally or due to surgical removal (Beavis, Brown & Smith 1969; Fraser et al. 1973). Receptors for prostaglandin F2α are present on the surface of the luteal cell (Powell, Hammarstrom, Samuelsson & Sjoberg 1974) and it has been suggested that luteal regression may be due to the local production of PGF2α, a substance known to be responsible for luteal regression in sheep and guinea pigs (Goding 1974). However, the concentration of PGF2α within the corpus luteum shows no rise until after luteal regression is already complete (Swanston, McNatty & Baird 1976). Moreover, although PGF2α will inhibit progesterone secretion when added to cultures of human granulosa cells (McNatty, Henderson & Sawyers 1975), attempts to induce premature luteal regression by infusion of PGF2α in vivo have been inconclusive (Wentz & Jones 1974). This may be due to the difficulty of delivering enough PGF2α locally to the ovary due to its rapid extraction from the blood by the lungs and liver.
Menstrual cycle

The endometrium exhibits a well described cycle induced by ovarian hormones (Corner 1951). Under the influence of oestradiol the endometrial glands and stroma proliferate during the first half of the cycle. After ovulation the combined secretion of oestradiol and progesterone from the corpus luteum induces secretory changes in the glands so that the glandular lumen becomes filled with secretions composed of glycoproteins. The coordinated development of a secretory endometrium is necessary if implantation of the blastocyst is to occur normally within the uterus. In the non-pregnant cycle, the falling levels of oestradiol and progesterone from the regressing corpus luteum induce a series of changes in the endometrium which result in menstruation within 2–3 days.

The exact sequence of events in the endometrium which lead to menstruation have been observed in the rhesus monkey (Markee 1940). As the levels of ovarian hormones fall, the endometrium shrinks and vascular stasis occurs as the spiral arterioles supplying the endometrium become more convoluted. A period of vasodilation with extravasation of blood into the perivascular spaces is followed by intense vasoconstriction of the coiled arteries at the point where they leave the myometrium and enter the endometrium. The resulting tissue ischaemia and damage is followed within 4–24 h by sloughing of the superficial two-thirds of the endometrium together with some bleeding. The mechanism of menstruation is still unknown although the endometrium is known to synthesize a number of potent vasoactive substances including prostaglandins (Pickles 1957). The concentration of PGF2α and PGE2 in the endometrium increase markedly during the luteal phase of the cycle and reach their highest levels during menstruation (Downie, Poyser & Wunderlich 1974).

Although endometrial bleeding can occur due to withdrawal of oestrogen alone, as in an anovulatory cycle, it appears that both oestrogen and progesterone are necessary for normal menstruation. Anovulatory cycles tend to be very irregular in length and the quantity of bleeding can vary considerably (Wallach 1970). For this reason any form of contraception which results in anovulatory cycles is likely to be associated with an unacceptably high incidence of irregular menstruation.

Manipulation of the menstrual cycle

It is convenient to classify methods of contraception as to whether they act primarily at the level of the hypothalamic-pituitary system, the ovary or the uterus (table 1).

Inhibition of hypothalamic-pituitary system

Exogenous ovarian steroids, e.g. oestrogens and progestagens, act primarily by inhibiting the release of gonadotrophins (Klopper 1970). Follicular development can be inhibited by oestrogens given early in the follicular phase (Vaitukaitis et al. 1971). If oestrogens are given after day 8, ovulation still occurs indicating that by
this stage the follicle is relatively independent of endogenous gonadotrophin (Østegaard & Starrup 1968). Because breakthrough bleeding and menstrual irregularity often occur with oestrogen alone, gestagen is added to oestrogen and this forms the basis for the combined oral contraceptive pill. Both the basal level of FSH and LH and the mid-cycle peak of LH are suppressed by the combined pill so that ovarian stimulation is minimal (Klopper 1970). The uterus is exposed to a constant ratio of oestrogen and gestagen, and withdrawal bleeding after stopping the pill is often lighter than normal. One of the reasons for the popularity of the combined pill is the fact that the onset of menstrual bleeding is entirely predictable. Moreover, if the expected time of bleeding is socially inconvenient menstruation can be delayed merely by continuing the pill. There is little doubt that if menstruation is considered desirable, the combined pill, in spite of the slight risk of thromboembolic complications (Vessey & Doll, this publication), offers a very successful and effective form of contraception as attested by its widespread acceptance throughout the world.

**Table 1. Methods of contraception**

(1) Hypothalamus and anterior pituitary  
(a) Inhibition of gonadotrophins  
\quad e.g. combined oestrogen/gestagen pill  
\quad large doses of gestagen  
\quad analogues of LHRH  
(b) Inhibition of positive feedback  
\quad e.g. medium dose gestagen

(2) Ovary  
(a) Inhibition of follicle rupture  
\quad e.g. inhibitors of PG synthesis  
(b) Suppression of luteal function  
\quad e.g. large doses oestrogen and gestagens  
\quad ?prostaglandin F2α or analogues

(3) Uterus  
(a) Inhibition of implantation  
\quad e.g. intra-uterine devices  
(b) Inhibition of sperm transport and/or fertilization  
\quad e.g. low dose gestagen  
(c) Inducers of menstruation  
\quad e.g. ?prostaglandins

The usual system of prescribing the combined pill in a monthly cycle has the advantage that withdrawal bleeding is a periodic reassurance to the woman that conception has been avoided. However, some success has been obtained on a three monthly cycle (Short, this volume) although whether it would find widespread acceptance is unknown. Long acting gestagens (e.g. medroxyprogesterone) given by intramuscular injection or by subcutaneous silastic implant in large doses suppress gonadotrophins and hence follicular development (Mishell *et al.* 1974; Johansson, this volume). However, in lower doses follicular development still occurs, although ovulation is prevented by inhibiting the ability of oestrogen to
induce an LH surge (Larrson-Cohn, Johansson & Gemzell 1970). This failure of positive feedback results in anovulatory cycles which may be manifest in irregular breakthrough bleeding or multiple follicular cysts.

The dose of gestagen given in some continuous gestagen régimes may be insufficient to inhibit LH discharge and hence ovulation may occur (Larrson-Cohn, Johansson, Wide & Gemzell 1970; Diczfalussy et al. 1969). The contraceptive action of these compounds is presumed to be due to their effect on cervical mucus and possibly the endometrium. Although the toxicity of this form of contraception is low, menstrual irregularity is common and the overall effectiveness is poor.

All the steroidal contraceptives in present use have intrinsic oestrogenic or progestational properties and hence an effect on the uterine endometrium. There would be considerable advantages in a compound which while inhibiting the release of gonadotrophins, had no stimulatory effect on the uterus and hence caused endometrial atrophy. Most androgens will cause amenorrhoea in this way (Papanicolaou, Ripley & Shaw 1939) but have side effects, e.g. hirsutism, which prevent their use as contraceptives. However, a synthetic derivative (2-3-ixosol) of 17α-ethinyltestosterone (Danazol) can inhibit gonadotrophins but apparently has very little intrinsic oestrogenic, progesterational or androgenic properties (Greenblatt, Borenstein & Hernandez-Ayup 1974). The development of a cheap, non-toxic compound with similar properties to Danazol would offer a very effective form of contraception.

Another means of inhibiting the release of gonadotrophins is to antagonize the synthesis, release or activity of luteinizing hormone releasing hormone (LHRH). LHRH can be made immunogenic by coupling to an appropriate protein and ovulation has been inhibited in rabbits immunized against LHRH (Fraser 1975). Various synthetic analogues of LHRH have been shown to act as competitive inhibitors presumably by occupying the receptors for LHRH in the pituitary cells responsible for the synthesis and release of gonadotrophins (Coy et al. 1974; Vilchez-Martinez et al. 1975). These techniques result in a hypogonadotrophic state and associated amenorrhoea. Whether they will be useful as a practical form of contraception will depend on whether amenorrhoea is acceptable to women as well as whether they are non-toxic and their effects are reversible (Miller & Smith 1975).

Another way of inhibiting the release of gonadotrophins and ovulation is to suppress the activity of the hypothalamic centres responsible for the synthesis of releasing hormone. This occurs physiologically during lactational amenorrhoea which is characterized by ovarian inactivity due to lack of gonadotrophic stimulation. There is considerable evidence from experimental animals that hypothalamic function is suppressed by the afferent stimuli of suckling. It is well known that ovarian activity and fertility is restored more rapidly following parturition if lactation is suppressed (see Short, introductory chapter). If the mammary gland is denervated in sheep ovarian activity returns in spite of continued suckling of lambs, indicating that the inhibition of gonadotrophin release is due to an afferent neural stimulus from the mammary gland (Kann & Martinet 1975).
In the majority of women who present clinically with secondary amenorrhoea, the failure of ovarian activity is due to a functional suppression of hypothalamic activity (Baird & Fraser 1973). Compounds such as reserpine and chlorpromazine which deplete the levels of catecholamines in the brain, may result in amenorrhoea and galactorrhoea due to failure of hypothalamic activity. Other precipitating factors such as weight loss, psychological stress, and the oral contraceptive pill are presumed to operate through central mechanisms. Unfortunately we do not know enough about the normal control of hypothalamic function to be able to manipulate the central control of gonadotrophin release without affecting other hypothalamic functions. But in many ways the woman with secondary amenorrhoea due to lactation or idiopathic hypothalamic suppression is in an ideal contraceptive state.

**Follicle rupture**

As mentioned previously the mechanism of ovulation is poorly understood. If the synthesis of prostaglandins is necessary in women for rupture of the pre-ovulatory follicle, as in experimental animals, it should be possible to prevent ovulation by inhibitors of prostaglandin synthesis. If the endocrine function of the luteinized follicle containing the trapped oocyte is similar to the corpus luteum, a normal menstrual cycle would result. The drugs which are currently available for inhibiting synthesis of prostaglandin are either too toxic (e.g. indomethacin) or must be given in too high a dose (e.g. aspirin) to be used as a routine contraceptive. However, inhibition of follicle rupture would seem a promising field for future research.

**Luteal function**

Because the corpus luteum is necessary for the maintenance of the early stages of gestation an attractive form of contraception would appear to be interference with luteal function (Jewelewicz et al. 1973). Unfortunately it seems that a normal corpus luteum is also necessary for regular menstruation. Thus attempts to produce inadequate function of the corpus luteum by interference with the normal development of the follicle (Vaitukaitis et al. 1971) are associated with menstrual cycles of irregular length and duration. For the same reason although progesterone secretion from the corpus luteum can be inhibited by relatively large doses of gestagens (Johansson 1971), oestrogens (Johansson & Gemzell 1971) and other steroids such as oxymethalone (Klaiber, Henzl, Lloyd & Segre 1973) it is unlikely that this approach will ever be widely used as a contraceptive. The induction of premature menstrual bleeding with prostaglandin F2α is probably due to its effect directly on the uterus rather than to a luteolytic effect in the corpus luteum (Wentz & Jones 1973; Karim & Hillier 1975).

Although inhibition of luteal function is unlikely to be accepted for routine use, it may be useful in order to prevent pregnancy when intercourse is infrequent.
Thus post-coital oestrogens have been used successfully to prevent pregnancy following rape.

_Uterus_

If a pregnancy is to occur, the fertilized ovum must survive in the fallopian tubes and uterine cavity before the blastocyst implants in the uterus some seven to nine days after ovulation. The correct uterine environment is thought to be essential for normal development of the early embryo. It has already been mentioned that many of the contraceptive steroids produce direct effects on the uterus and cervix which impair fertility. Embryo transfer experiments in laboratory and domestic animals show that ovarian cycles must be carefully synchronized if the donor embryo is to develop in the uterus of the recipient successfully (Polge 1972). In the absence of definitive evidence to the contrary it is reasonable to assume that the same requirements apply in the human female.

In spite of the obvious advantages of such an approach relatively few methods aimed primarily at disrupting the uterine environment are used in clinical practice. The intra-uterine device produces a low grade inflammatory reaction within the uterus and is thought to exert its contraceptive effect by preventing implantation (Eckstein 1970). The presence of an i.u.d. in animals has been shown to stimulate the production of prostaglandins by the endometrium and the relative frequency of irregular menstruation may be due to this property.

Menstruation is normally the sign of a sterile cycle and any factor which will induce endometrial bleeding could be used as a contraceptive. The naturally occurring prostaglandins F2α and E2 have been used with limited success as a ‘menstrual inducer’ when administered by intravaginal pessary within a few days of the expected period (Karim 1971). However, they are not a hundred per cent effective, and while it was hoped that some of the longer acting derivatives, e.g. 15-methyl-PGE2 (Yankee & Bundi 1972), might have fewer side effects at a therapeutic dose, the results so far have been disappointing. A new class of 16-aryloxyprostaglandins have been shown to be 200 times more potent than PGF2α at producing luteal regression in experimental animals while at the same time equipotent on smooth muscle (Binder et al. 1974; Dukes, Russell & Walpole 1974). Whether these compounds show the same dissociation of biological properties in human beings remains to be seen.

_Future prospects_

In the last ten years no new form of contraceptive as effective and as widely acceptable as the combined pill has been developed in spite of intensive research. Yet if we consider the states of infertility which occur naturally throughout a woman’s life (table 2) we have only managed to mimic pregnancy (and the luteal phase of the cycle) with the combined pill as an effective form of contraceptive. If we knew more about the mechanism of normal luteal maintenance and regression, it might be possible to induce a prolonged state of ‘pseudopregnancy’.
Manipulation of the Menstrual Cycle

The only other form of contraceptive which mimics a natural period of reduced fertility is the 'continuous gestagen only' pill which by inhibiting positive feedback results in a series of anovulatory cycles similar to those seen at the extremes of reproductive life. However, these anovulatory cycles result in a high morbidity due to irregular menstruation and it is unlikely for this reason that any form of compound which only inhibited positive feedback would ever be acceptable.

Table 2. Physiological Periods of Infertility

<table>
<thead>
<tr>
<th>Age</th>
<th>Reason for Infertility</th>
<th>Mechanism</th>
<th>Contraceptive Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pubertal</td>
<td>Follicular immaturity</td>
<td>Hypothalamus very sensitive to negative feedback</td>
<td>None</td>
</tr>
<tr>
<td>Post-menarchal luteal phase</td>
<td>Failure of ovulation</td>
<td>Failure of positive feedback</td>
<td>Gestagen only</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Follicular immaturity</td>
<td>Hypogonadotrophic</td>
<td>Combined 'pill'</td>
</tr>
<tr>
<td>Lactation</td>
<td>Follicular immaturity</td>
<td>Suppression of hypothalamic activity</td>
<td>None</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>Ovarian failure</td>
<td>Lack of oocytes</td>
<td>None</td>
</tr>
</tbody>
</table>

Ovarian failure occurs in most women between 45–55 years at the menopause due to depletion of the stock of available oocytes. Premature ovarian failure can occur spontaneously or secondary to treatment with X-irradiation or cytotoxic drugs. There is a higher incidence of premature ovarian failure in so-called autoimmune diseases such as Addison’s Disease (Irvine 1970) and antibodies to ovarian cells can be demonstrated in a proportion of these patients. The induction of ovarian failure by active immunization against antigens present in the oocyte is theoretically a possible method of contraception but is unlikely to be practical. The incidence of senile osteoporosis and atrophy of genital tract is much higher in patients with premature ovarian failure and would necessitate the administration of oestrogens as replacement therapy.

For the future the most rewarding means of manipulating the menstrual cycle for contraceptive purposes would appear to be aimed at altering the level of hypothalamic activity. Pre-pubertally the hypothalamus is exquisitely sensitive to the negative feedback effects of oestrogen so that release of gonadotrophins is inhibited by minimal amounts of ovarian oestradiol (Kulin, Grumbach & Kaplan 1969). Hence development of the primordial follicle into a mature Graafian follicle is prevented. The relative ovarian inactivity which occurs during lactational amenorrhoea is probably due to lack of stimulation by gonadotrophins. Hypothalamic activity is suppressed by an afferent neural reflex induced by the stimulation of the nipple during suckling (Kann & Martinet 1975). We know little about the mechanisms involved in determining the activity of the hypothalamus or how its sensitivity to steroid feedback is set. Certain drugs such as reserpine and phenothiazines which deplete the brain of dopaminergic amines can induce a hypogonadotrophic state and infertility (Baird & Fraser 1973). Unfortunately they are too unpredictable and toxic to be used as contraceptives but a safe and reversible
means of achieving a state of hypothalamic suppression as in lactation or during childhood, would probably be an ideal form of contraception. The ovaries would be ‘ticking over’ producing enough oestrogen to prevent genital atrophy and other signs of oestrogen deficiency but not enough to stimulate menstrual bleeding.

Whether women would find the resulting amenorrhoea acceptable is a subject for future research but the saving in blood loss alone would be an obvious health advantage, especially in those areas of the world where anaemia due to malaria, hookworm, etc. is endemic.

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