Ovarian feedback, mechanism of action and possible clinical implications

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The secretion of gonadotrophins from the pituitary in women is under ovarian control via negative and positive feedback mechanisms. Steroidal and non-steroidal substances mediate the ovarian effects on the hypothalamic-pituitary system. During the follicular phase of the cycle, estradiol (E₂) plays a key role, while circulating progesterone (at low concentrations) and inhibin B contribute to the control of LH and FSH secretion respectively. During the luteal phase, both E₂ and progesterone regulate secretion of the two gonadotrophins, while inhibin A plays a role in FSH secretion. The intercycle rise of FSH is related to changes in the levels of the steroidal and non-steroidal substances during the luteal-follicular transition. In terms of the positive feedback mechanism, E₂ is the main component sensitizing the pituitary to GnRH. Activity of a non-steroidal ovarian substance, named gonadotrophin surge-attenuating factor (GnSAF), has been detected after ovarian stimulation. It is hypothesized that GnSAF, by antagonizing the sensitizing effect of E₂ on the pituitary, regulates the amplitude of the endogenous LH surge at midcycle. Disturbances in the feedback mechanisms can occur in various abnormal conditions or after treatment with pharmaceutical compounds that interfere with the production or the action of endogenous hormones.

Key words: FSH/LH/estrogen/ovarian feedback/progesterone
secretion of FSH and LH is differentially controlled by the ovaries (Dafopoulos et al., 2004a). In a series of experiments in which two simulated follicular phases and one simulated luteal phase in between were artificially induced in estrogen-deprived post-menopausal women by exogenous administration of estrogen and progesterone, the elevated serum FSH and LH concentrations gradually declined as $E_2$ and progesterone values increased. Although by the end of the simulated luteal phase, the levels of LH had been suppressed to the normal premenopausal range, those of FSH were still higher than in the early follicular phase of the normal menstrual cycle (Dafopoulos et al., 2004a). This suggests that $E_2$ plus progesterone only partly affect FSH secretion and that other already known ovarian substances may also be important as will be discussed in the next section on non-steroidal hormones. In the same study, however, during the second simulated follicular phase, the already reduced levels of FSH remained stable, while those of LH increased gradually despite the increasing concentrations of $E_2$ (Dafopoulos et al., 2004a). It is suggested from these data that $E_2$ regulates differentially FSH and LH secretion in women.

The inability of follicular phase $E_2$ levels to maintain low LH levels in the presence of non-functioning ovaries suggests that during the normal follicular phase this steroid is not the only mediator of the ovarian negative feedback effect on LH secretion. It is likely that endogenous progesterone also contributes, because in the above experiments serum concentrations of this steroid were lower in the post-menopausal women than in the normal follicular phase (Dafopoulos et al., 2004a). Furthermore, treatment of normal women with the antiprogestagen, mifepristone, during the early- and midfollicular phases of the cycle results in a significant increase in basal LH levels (Kazem et al., 1996). So far, no other studies have particularly investigated the ability of progesterone, in concentrations normally found in the follicular phase of the cycle, to control gonadotrophin secretion in women. In one study, exogenous administration of this steroid to women with polycystic ovary syndrome (PCOS) resulted in a significant reduction of the already elevated serum LH concentrations, but only luteal phase progesterone levels were achieved (Buckler et al., 1992).

Progesterone is normally produced by luteinizing granulosa and by luteal cells. Although the source of its production during the follicular phase has not been clarified, one study has suggested the adrenal gland (Judd et al., 1992). However, it has been shown more recently that following ovariectomy, performed in the midfollicular phase of the cycle, serum concentrations of progesterone declined to almost unmeasurable concentrations (Alexandris et al., 1997). This suggests that the ovaries produce progesterone even during the follicular phase of the cycle. The fact that in the same study (Alexandris et al., 1997) as well as in previous studies (Wallach et al., 1970; Yen and Tsai, 1971a; Monroe et al., 1972b; Daw, 1974; Chakravarti et al., 1977; Muttukrishna et al., 2002) serum $E_2$ levels also declined, while FSH and LH levels increased gradually following ovariectomy, provides evidence that endogenous ovarian steroids are important for the control of gonadotrophin secretion.

Ovarian stimulation for IVF is an alternative way to study the role of endogenous estrogens in gonadotrophin secretion. It has been shown that during induction of multiple follicular development with the use of FSH, a rapid decline in the concentrations of basal LH occurs, while $E_2$ concentrations rise to supraphysiological levels (Messinis and Templeton, 1987a; Messinis et al., 1998). At least two studies have suggested that it is the rising $E_2$ that suppresses LH levels on this occasion. In one of them (Messinis et al., 1994), a single FSH dose of 450 IU, injected to normal women on cycle day 2, resulted in a temporal but significant increase in serum $E_2$ values and in a concomitant suppression of basal LH values.

In the second study (Messinis and Templeton, 1989), normally cycling women were treated in one cycle with clomiphene citrate and in another cycle with daily injections of FSH. In both cycles, serum $E_2$ concentrations increased to supraphysiological levels, but LH levels were suppressed only in the FSH-treated cycles, while in the clomiphene cycles they increased significantly. These two studies provide evidence that the suppressing factor of LH levels during treatment with FSH is endogenous $E_2$, which in the case of clomiphene was unable to act due to the occupation of estrogen receptors. The site of action of estrogen is primarily the pituitary; however, an effect on the hypothalamus cannot be excluded (Nakai et al., 1978; Plant et al., 1978; Kelner and Peck, 1984; Richardson et al., 1992).

Although $E_2$ plays a predominant role in the control of gonadotrophin secretion during the follicular phase, this has not been universally acknowledged. One of the reasons is possibly the fact that despite elevated FSH in normally cycling women, towards the end of their reproductive life, circulating $E_2$ levels remain within the normal range (Lee et al., 1988). In addition, a recent study showed that while serum $E_2$ values on cycle days 3–5 of normally menstruating women aged 40–50 years correlated negatively with FSH, inhibin B was the only independent predictor of FSH values (Burger et al., 2000).

The role of non-steroidal ovarian hormones

Along with the steroids, the ovaries produce non-steroidal substances, such as inhibins (Bicsak et al., 1986; Roberts et al., 1993). These proteins by definition suppress only basal FSH secretion from the pituitary. Although in vitro data have shown that under specific circumstances LH secretion may be also affected (Farnworth et al., 1988), this hormone is much less sensitive to inhibition than FSH (Attardi et al., 1991). It has been suggested that during the follicle selection process, the follicle destined to become dominant produces inhibin B (de Kretser et al., 2002), the levels of which are high in the early- to midfollicular phases and very low in the late follicular and luteal phases (Groome et al., 1996). In contrast, the levels of inhibin A are low in the follicular phase and rise markedly during the luteal phase, indicating that this form is produced mainly by the corpus luteum (Groome et al., 1996).

In terms of the role of inhibin in the secretion of gonadotrophins, there is little evidence in humans, and only animal data have convincingly indicated that this protein participates in the control of FSH secretion in vivo. In particular, immunoneutralization of inhibin by the injection of antibodies to rats resulted in a significant increase in FSH levels (Rivier et al., 1986). Also, administration of inhibin antiserum to rats and hamsters increased FSH-β mRNA without affecting LH-β (Attardi et al., 1992; Kishi et al., 1996). In addition, administration of recombinant inhibin A to rats or to castrated rams blocked the FSH surge and suppressed plasma FSH levels respectively (Rivier et al., 1991; Tilbrook et al., 1993). Finally, in rhesus monkeys, inhibin A given during the early follicular phase rapidly decreased circulating FSH levels (Stouffer et al., 1994; Molsnæss et al., 1996).
Data in humans only indirectly indicate that inhibin participates in the control of FSH secretion. In one study, in which normally cycling women were treated with clomiphene for 15 days during the follicular phase, LH levels increased continuously throughout the treatment, while those of FSH after an initial rise declined to the pretreatment levels (Messinis and Templeton, 1988b). As clomiphene is an anti-estrogenic compound, it is suggested that for the control of FSH secretion, non-estrogenic mechanisms are also important, supporting the hypothesis of inhibin participation. In post-menopausal women, elevated FSH declines during treatment with estrogen but never returns to premenopausal levels suggesting that inhibin may be missing in these women (Lind et al., 1978; Dafopoulos et al., 2004a).

Recent studies in normally cycling premenopausal women have shown a significant decline in inhibin, E2 and progesterone concentrations following ovariectomy (Alexandris et al., 1997; Muttukrishna et al., 2002). When the operation was performed in the follicular phase, the levels of both inhibin A and inhibin B decreased significantly, but when it was performed in the luteal phase only inhibin A declined (Muttukrishna et al., 2002). These data confirm that inhibin B is mainly produced in the follicular phase and inhibin A in the luteal phase but do not provide a clear relationship between these hormones and FSH. Nevertheless, when older perimenopausal but normally cycling women with increased early follicular FSH levels were compared with younger women with normal FSH levels, it was found that the older women also had lower inhibin B but similar inhibin A concentrations (Klein et al., 1996; Burger et al., 1998; Klein et al., 2004). Furthermore, in women with imminent premature ovarian failure, but with ovulatory cycles, persistently elevated FSH was accompanied by reduced levels of inhibin B and inhibin A (Welt et al., 2005a). It is likely from these data that inhibin plays a role in the ovarian negative feedback control of FSH secretion in women. However, inhibin B is particularly important during the follicular phase of the cycle (Table I).

The role of other non-steroidal substances, such as activin and follistatin, is less clear. Activin is a dimeric product of the β-subunit of inhibin and exists in three forms, ‘A’, ‘B’ and ‘AB’ (Muttukrishna et al., 2004). Animal data have shown that activin stimulates the secretion of FSH from pituitary cells in culture (Ling et al., 1986; Vale et al., 1986) as well as in vivo (McLachlan et al., 1989; Rivier and Vale, 1991; Stoever et al., 1993), and therefore, this protein does not have a place in the negative feedback mechanism. In women, due to methodological difficulties, only activin A has been measured in blood during the normal menstrual cycle, and the data have shown fluctuations with higher levels in the early follicular phase, at midcycle and in the late luteal phase (Muttukrishna et al., 1996). The importance of these changes is not clear, although activin A may contribute to the increase in FSH levels at these particular periods.

Follistatin was initially thought to be an inhibin agonist (Robertson et al., 1987; Ueno et al., 1987), but it was subsequently found to be a binding protein for activin that may have no other specific biological roles (Nakamura et al., 1990). Most circulating follistatin in cycling women is activin bound (McConnell et al., 1998). Data in animals, however, have shown that follistatin may exert actions on FSH secretion in vivo. In particular, administration of human recombinant follistatin-288 to ovariecotomized rams reduced the secretion of FSH but not LH (Tilbrook et al., 1995). Also, in a study in ewes, it was shown that the same recombinant product was able to suppress FSH levels in the peripheral circulation without affecting basal GnRH secretion or the frequency and the amplitude of GnRH pulses (Padmanabhan et al., 2002). The mechanism of this effect is unclear but is possibly related to the bioavailability of activin (Padmanabhan et al., 2002).

Data on the mechanism of action of inhibin are lacking in women, and information is derived only from studies in animals. It has been suggested that in the context of the negative feedback mechanism, inhibin acts directly on the pituitary without affecting GnRH secretion, although it may reduce the GnRH-induced FSH secretion (de Kretser et al., 2002). However, the existence of inhibin/activin and follistatin subunits in the pituitary cells of various species indicates that these proteins may also exert local effects (Mather et al., 1992; Bilezikjian et al., 1993; Farnsworth et al., 1995). Especially, activin A has been shown to be secreted by rat anterior pituitary cells in culture (Liu et al., 1996a), whereas activin B is the major form in such cells (Bilezikjian et al., 1994). It is possible, therefore, that the effect of these proteins on FSH secretion is exerted via antocrine/paracrine pathways (Corrigan et al., 1991). Follistatin is also secreted from rat pituitary cells (Liu et al., 1996b), and therefore, its inhibitory effect on FSH secretion may be via the neutralization of pituitary activin (Ling et al., 1986; Vale et al., 1986; Muttukrishna and Knight, 1991).

The role of another non-steroidal substance named anti-Mullerian hormone (AMH) is less clear. In women, AMH is expressed in the granulosa cells of follicles from the primordial to the antral stage until the size of 4–6 mm (Weenen et al., 2004). Although it appears that serum levels of AMH on cycle day 3 of normally cycling women decline with increasing age (de Vet et al., 2002) and show a negative correlation with FSH (van Rooij et al., 2002), its role in the ovarian negative feedback system has not been clearly established.

### Table I. Ovarian hormones that mediate the negative feedback effect on FSH and LH secretion in women

<table>
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<tr>
<th>Follicular phase</th>
<th>Luteal phase</th>
<th>Luteal-follicular transition (intercycle rise of FSH)</th>
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**Luteal phase**

During the luteal phase, the increased values of progesterone and \( E_2 \) play an important role in the maintenance of the low FSH and progesterone.
Although in that study E2 and progesterone levels also declined, a significant increase in serum FSH concentrations (Muttukrishna et al., 1994). A recent study in women has shown a significant decline in FSH, however, inhibin may participate in the control of gonadotrophin secretion during the luteal phase but does not affect the role of each of them. The latter has been further investigated in a recent study (Messinis et al., 2002) demonstrating that maintenance of midluteal levels of E2 with the administration of exogenous estrogen immediately after ovariectomy postponed the expected increase in FSH and LH concentrations by on average 3 days. When, however, the midluteal concentrations of progesterone were also maintained with the exogenous administration of this steroid, the increase in FSH and LH values was prevented (Messinis et al., 2002). This suggests that it is the combined action of E2 and progesterone that mediates the negative feedback effect of the ovaries on gonadotrophin secretion during the luteal phase of the cycle. Whether progesterone alone could express a similar action has not been investigated, although under experimental conditions the negative feedback effect of progesterone is apparent in the presence of estrogen (Soules et al., 1984).

During the luteal phase, the frequency of GnRH pulses decreases, while the amplitude increases (Filicori et al., 1986). Although this could be due to the high progesterone concentrations (Soules et al., 1984), it seems that both E2 and progesterone are required to maintain this pattern (Nippoldt et al., 1989). The suppressing effect of these two steroids on gonadotrophin secretion is possibly mediated via an increase in β-endorphin activity in the hypothalamus (Wehrenberg et al., 1982).

Apart from the steroids, no other ovarian substances have been detected to specifically suppress basal LH secretion in women. For FSH, however, inhibin may participate in the negative feedback mechanism during the luteal phase but does not affect LH secretion. This is derived from data in both animals and women. Infusion of inhibin A into rhesus macaques starting at midluteal phase resulted in a progressive decline in FSH levels (Stouffer et al., 1994). A recent study in women has shown a significant decline in inhibin A values within the first 12 h from ovariectomy performed in the luteal phase that was followed by a gradual but significant increase in serum FSH concentrations (Muttukrishna et al., 2002). Although in that study E2 and progesterone levels also declined, a negative correlation between the values of inhibin A and FSH was found. In the same study, inhibin B levels did not change significantly after ovariectomy, suggesting that this protein is not a regular component of the negative feedback mechanism during the luteal phase of the cycle (Muttukrishna et al., 2002). Nevertheless, previous data have demonstrated that normally cycling premenopausal women with raised FSH values in the early follicular phase had during the luteal phase inhibin A, and during the follicular phase inhibin B, concentrations significantly lower than in women with normal FSH levels (Danforth et al., 1998; Santoro et al., 1999; Welt et al., 1999; Muttukrishna et al., 2000). These data provide evidence that both forms of inhibin participate in the control of FSH secretion in women with inhibin A being important during the luteal phase and inhibin B during the follicular phase of the cycle.

The role of activin and follistatin in the control of human gonadotrophin secretion during the luteal phase is, as in the follicular phase, not clear. Measurement of follistatin in the circulation of women has not shown any significant alterations throughout the whole menstrual cycle (Khoury et al., 1995; Kettel et al., 1996; Evans et al., 1998).

**Luteal-follicular transition**

During the passage from the luteal to the next follicular phase, an increase, or ‘intercycle rise’, in serum FSH concentrations occurs. FSH starts to increase 2–3 days before the onset of the menstrual period, although recent data have shown that the initial rise occurs 4 days before menses (Miro and Aspinall, 2005). FSH remains elevated during the early follicular phase and returns to the basal value in midfollicular phase (Maires et al., 1987; Messinis et al., 1993c). During the period of FSH increase, also named the ‘FSH window’, the selection of the dominant follicle takes place. The described changes in FSH levels were measured by immunnoassays, but when a specific in vitro bioassay was used, increased signal was detected earlier, i.e. in midluteal to late luteal phase (Christin-Maitre et al., 1996).

The intercycle rise of FSH appears to be controlled by ovarian substances (Figure 1). Before the onset of the FSH rise, a gradual but significant decline in the levels of inhibin A, E2 and progesterone takes place (Roseff et al., 1989; Groome et al., 1996). It is assumed, therefore, that the intercycle rise of FSH starts in late luteal phase as a result of the reduced activity of the negative feedback mechanism that suppressed FSH secretion during the early- and midluteal phase.

**Figure 1.** Hormonal dynamics during the luteal-follicular transition. The FSH intercycle rise is the result of the reduced activity of the negative feedback mechanism due to the decrease in estradiol (E2), inhibin A and progesterone (P4) concentrations in late luteal phase. The FSH increase is terminated by the rising E2 and inhibin B levels produced by the dominant follicle. The diagram, regarding the pattern of hormonal changes, is based on data presented in two references (Messinis et al., 1993c; Groome et al., 1996).
phases. Inhibin B does not participate in this mechanism. However, from the time FSH levels reach a peak at the onset of menstruation, inhibin B levels increase gradually and significantly (Groome et al., 1996). It is possible that the increasing concentrations of inhibin B under the influence of FSH during the early follicular phase (Welt et al., 1997) suppress FSH secretion, narrowing thus the FSH window.

Based on these data, it is assumed that both forms of inhibin are important for the control of FSH secretion during the intercycle period in women with inhibin A playing a role in the process that ‘opens’ and inhibin B in the mechanism that ‘closes’ the FSH window (Table 1). Although this makes sense, a study in women has shown that maintenance of midluteal concentrations of E2 during the intercycle period postponed the intercycle rise of FSH despite a decline in inhibin concentrations (Le Nestour et al., 1993). Furthermore, following the selection of the dominant follicle in the normal cycle, serum FSH declined as E2 levels increased (van Santbrink et al., 1995). It is suggested from these results that E2 is possibly more important than inhibin in regulating the FSH window. More recent data in women treated with the anti-estrogenic compound, tamoxifen, have confirmed the greater role of E2 over inhibin in the negative control of FSH secretion during the luteal phase and the luteal-follicular transition with inhibin B being more important as the follicular phase progresses (Welt et al., 2003).

The role of progesterone in the control of the intercycle rise of FSH is less clear, although this hormone may participate via an effect on GnRH secretion. Progesterone is believed to reduce the frequency and increase the amplitude of LH pulses during the luteal phase of the cycle (Soulès et al., 1984; Nippoldt et al., 1989). Therefore, the withdrawal of the progesterone effect in late luteal phase increases the frequency of GnRH pulses (McCartney et al., 2002), an event that stimulates predominantly the secretion of FSH (Marshall and Kelch, 1986; Hall et al., 1992). This is possibly one of the reasons that the increase of LH during the intercycle period is less discernible. In any case, however, the frequency of GnRH pulses contributes to but is not solely responsible for the intercycle rise of FSH in women (Welt et al., 1997).

Another mechanism that might contribute to the intercycle rise of FSH includes activin A. The concentrations of this protein, despite limitations in the existing methodology, start to increase from the midluteal phase, preceding through the intercycle rise of FSH (Muttukrishna et al., 1996). Also, aged but normally cycling women with raised FSH values in the early follicular phase had increased concentrations of activin A in the luteal phase (Muttukrishna et al., 2000). Similarly, a significant increase in serum activin A levels over age has been reported in healthy postmenopausal women (Baccarelli et al., 2001). In terms of the role of other forms of activin, such as activin B and activin AB, there are no data in the literature regarding their concentrations in the circulation of women.

Positive feedback mechanisms

It has been known for years that E2 is the main component of the positive feedback effect of the ovaries on the hypothalamic-pituitary system (Ferin et al., 1974). This steroid sensitizes the pituitary to GnRH and enhances the self-priming action of GnRH on the pituitary gonadotrophs (Lasley et al., 1975). The interaction between E2 and GnRH is important for the expression of the endogenous gonadotrophin surge at midcycle (Hoff et al., 1977).

Pituitary sensitivity to GnRH

Experiments in women involving the i.v. infusion of GnRH or the i.v. administration of consecutive GnRH pulses have differentiated two functional pools of gonadotrophin secretion in the gonadotrophs (Lasley et al., 1975; Wang et al., 1976; Yen and Lein, 1976; Hoff et al., 1977). The first, also named ‘releasable’ pool, releases gonadotrophins immediately after stimulation by GnRH, whereas the second or ‘reserve’ pool, which represents the synthesis of new hormones, requires a longer stimulation by GnRH. Under these circumstances, the reserve is converted to the acutely releasable pool before gonadotrophins are secreted.

During the i.v. administration of two submaximal doses of GnRH, 10 μg each, to normal women 2 h apart, the response to the first pulse is maximum at 30 min and represents the pituitary ‘sensitivity’, while the whole area under the curve lasting 240 min represents the pituitary reserve (Lasley et al., 1975). The response to the second GnRH pulse is greater than the response to the first pulse, a pattern that is particularly evident in the presence of estrogen and is called ‘the self-priming effect’ of GnRH on the pituitary (Lasley et al., 1975; Wang et al., 1976; Hoff et al., 1979). Although this reflects increased number of GnRH receptors in the gonadotrophs (Laws et al., 1990), it may be also related to increased availability of GnRH in the pituitary as E2 inhibits GnRH metabolism by monkeys and rat pituitary cells (Danforth et al., 1990). In addition, data in rats have shown that GnRH controls LH biosynthesis by increasing glycosylation and polypeptide synthesis of LH, while E2 facilitates LH secretion by lowering the concentrations of GnRH needed to stimulate these two processes (Ramey et al., 1987). The biphasic pattern of LH response to GnRH has been also shown in vitro using rat pituitary cells in a perfusion system (Evans et al., 1983; Loughlin et al., 1984).

When GnRH experiments were performed during the human menstrual cycle, it was found that the pituitary sensitivity and reserve as well as the self-priming effect were augmented in the late follicular phase as compared to the early follicular phase (Wang et al., 1976; Hoff et al., 1977). This augmentation of LH secretion as a response to repeated injections of GnRH in an estrogenic environment is related to the rate with which LH molecules are discharged from the pituitary (Sollenberger et al., 1990), although the duration of the LH secretory events and consequently the LH mass are also augmented (Quyumi et al., 1993). It has been found that the pituitary sensitivity to GnRH, estimated as the 30-min response to a single i.v. GnRH dose of 10 μg, does not change significantly in women during the early- and midfollicular phases of the cycle, despite the significant rise in E2 concentrations, but increases markedly during the late follicular phase (Messinis et al., 1994; Messinis et al., 1998). This suggests that the sensitizing effect of E2 on the pituitary is inhibited during the early- and midfollicular phases and is facilitated in the late follicular phase of the normal menstrual cycle. Alternatively, the ovaries during the early- and midfollicular phases produce a substance that is able to antagonize the sensitizing effect of E2 on the pituitary gonadotrophs.

Experiments that were performed in healthy estrogen-deprived post-menopausal women support this assumption (Dafopoulos and the FSH window.
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et al., 2004a). In particular, two simulated follicular phases with a luteal phase in between were created in these women with the exogenous administration of E2 and progesterone. The experiments lasted for 43 days, and the pituitary sensitivity, expressed as the 30 min response to 10 μg GnRH i.v., was investigated on a daily basis. Immediately after the end of the simulated luteal phase, the response of LH to GnRH was similar to that in the early follicular phase of the normal menstrual cycle. However, from that point onwards, i.e. in the following simulated follicular phase a continuous increase in the pituitary sensitivity to GnRH was seen, which was different from that described in the normal follicular phase (Figure 2). These data are compatible with the hypothesis of a missing ovarian substance in the case of post-menopausal women because their ovaries are not functioning.

Such a substance could be gonadotrophin surge-attenuating factor (GnSAF) that in superovulated women reduces the pituitary response to GnRH and attenuates the endogenous LH surge (Messinis et al., 1985; Messinis and Templeton, 1989). Another candidate could be progesterone, but this is not likely because when normal women were treated with the antiprogestagen, mifepristone, both the pituitary sensitivity and reserve were significantly attenuated as compared to control cycles of the same women (Kazem et al., 1996). It is clear from these data that when the progesterone activity is neutralized, the pituitary sensitivity is decreased, and therefore, the lack of progesterone in the post-menopausal women would be expected to result in a decrease and not in an increase in the pituitary responsiveness to GnRH during the administration of E2. In other words, progesterone in the follicular phase of the normal cycle, although in low concentrations, probably sensitizes the pituitary to GnRH and in that way facilitates the E2 positive effect. In agreement with this notion are data in rats in which the sensitizing effect of progesterone on the GnRH self-priming in pituitary monolayers was abolished by coincubation with mifepristone (Byrne et al., 1996). Even, in the absence of progesterone, according to data in rats, GnRH self-potentiation requires a cross-talk with the progesterone receptor (Waring and Turgeon, 1992).

**LH surge onset**

As has been shown in several studies, E2 is the predominant factor that triggers the onset of the endogenous LH surge during the normal menstrual cycle provided a threshold level is exceeded for a certain period of time (Karsch et al., 1973; Keye and Jaffe, 1975; Young and Jaffe, 1976; March et al., 1979; Liu and Yen, 1983; Karande et al., 1990). It has been demonstrated that this level is around 200 pg/ml, and the period of pituitary exposure to it at least 48 h (Young and Jaffe, 1976; Simon et al., 1987; Karande et al., 1990). Even supraphysiological levels of E2 induced by the exogenous administration of estrogen are able to stimulate an LH surge (Messinis et al., 1992). The interaction of E2 with GnRH is important for the LH surge onset via an increased expression of the GnRH self-priming on the pituitary (Hoff et al., 1977).

The extent to which other ovarian hormones, such as progesterone, participate in the positive feedback mechanism at midcycle is less clear. Experiments in women have shown that progesterone can induce a positive feedback effect only after pretreatment with estrogen, even when the appropriate threshold for E2 has not been reached (Chang and Jaffe, 1978; March et al., 1979). At midcycle, the shift in steroidogenesis represents the ability of the preovulatory follicle to produce more progesterone than E2 (McNatty et al., 1979a,b). There has been debate, however, in the literature as to whether the progesterone secretion and, therefore, its concentrations in the circulation increase a little while before the onset of the midcycle LH surge (Johansson and Wide, 1969; Thorneycroft et al., 1974; Laborde et al., 1976; Landgren et al., 1977; Djahanbakhch et al., 1984). In one study, in which blood samples were taken from normal women every 2 h for 5 days during the periovulatory period, a clear increase in progesterone concentrations was demonstrated before the real onset of the surge (Hoff et al., 1983).

It is possible, therefore, that at midcycle the role of progesterone is permissive. In experiments performed in women, the administration of progesterone advanced the onset of an E2-induced LH surge (Chang and Jaffe, 1978; Liu and Yen, 1983; Messinis and Templeton, 1990). Also, in rats progesterone enhanced E2-induced GnRH secretion from the medial basal hypothalamus (Miyake et al., 1982), while the antiprogestagen, mifepristone, blocked the midcycle gonadotrophin surge in women when given after the emergence of the dominant follicle (Batista et al., 1992). Although the role of circulating progesterone in the positive feedback mechanism in women requires clarification, data in ovariectomized estrogen-treated progesterone receptor knockout mice have shown that activation of these receptors is necessary for the expression of the GnRH self-priming effect and the generation of the E2-induced gonadotrophin surge (Chappell et al., 2004a).

**Figure 2.** LH response to GnRH (ΔLH) in women. Comparison between (●) a simulated follicular phase (Group 1) and (▲) a control normal follicular phase (Group 2). In Group 1, estrogen-deprived post-menopausal women were treated with exogenous estradiol valerate and progesterone to induce concentrations of these two steroids similar to those in the follicular phase and the luteal phase of the normal menstrual cycle. Two simulated follicular phases and one luteal phase in between were induced. Days 32–42 correspond to the simulated luteal phase immediately after the simulated luteal phase. The changes in LH represent the pituitary sensitivity to GnRH (30 min response to an i.v. injection of 10 μg). The different pattern of LH changes is interpreted as indicating that the ovaries (Group 2) produce a substance (gonadotrophin surge-attenuating factor) that in the early follicular and midfollicular phases prevent the increase in pituitary sensitivity to GnRH. This substance was not produced in Group 1 as the ovaries were not functioning.*P < 0.05. Adapted from Dafopoulos et al., 2004a.
et al., 1999). Additional information in ovariectomized and adrenalectomized rats indicates that neuroprogesterone synthesized in the hypothalamus under the influence of E2 is an obligatory mediator of the positive feedback mechanism that is induced by this steroid (Micevych et al., 2003). Furthermore, data in rats have shown that estrogens induce de novo synthesis of progesterone from cholesterol in the hypothalamus, which plays a role in the onset of the LH surge (Soma et al., 2005). It is possible, therefore, that progestogenic mechanisms involving the progesterone receptor participate in the E2 positive feedback mechanism, regulating thus the LH surge onset.

The site of action of E2 for the positive feedback effect is both the hypothalamus and the pituitary (Xia et al., 1992). A preovulatory surge of GnRH has been detected in the ewe (Moenter et al., 1991). However, a LH surge has been induced by estrogens in monkeys with no GnRH production (Ferin et al., 1979). In women, while data are lacking, one study has shown an increase in plasma immunoreactive GnRH, as a result of estrogen administration, that precedes the increase of LH and FSH (Miyake et al., 1983). It is likely, therefore, that the primary site of the positive feedback effect is the pituitary and that GnRH plays a permissive role (Knobil, 1988). A recent study has shown that in rats a direct action of E2 on the anterior pituitary is obligatory for the positive feedback effect on LH secretion (Yin et al., 2002). Progesterone seems also to exert the positive feedback effect via the hypothalamus (Terasawa et al., 1982).

The mechanism of the E2 positive effect on gonadotrophin secretion is via the estrogen receptors (ER). Whether this involves ERα or ERβ or both is not clear. Both types exist in the gonadotrophs (Mitchner et al., 1998), while data in rats have shown that estrogens may regulate their own receptors as well as the pituitary responsiveness to them (Schreihofe et al., 2000). The effect of E2 is also mediated by changes in the activity of neurotransmitters in the hypothalamus, such as β-endorphin, whose plasma levels start to increase 2 days before the LH peak (Laatikainen et al., 1985).

**Characterization of GnSAF**

It has been suggested that GnSAF attenuates the endogenous LH surge and reduces the pituitary response to GnRH in superovulated women (Messinis et al., 1985, 1986; Messinis and Templeton, 1986, 1989) Whether GnSAF is similar to a gonadotrophin surge inhibiting factor (GnSIF) in monkeys (Sopelak and Hodgen, 1984) and rats (Geiger et al., 1980; Koppenaal et al., 1992) is not known. It may be that GnSAF and GnSIF share some structural similarities, although species differences may be important (Fowler and Templeton, 1996).

Attempts to purify GnSAF/GnSIF from various sources have shown molecular masses ranging from 12.5 to 69 kDa with different aminoacid sequences (Tio et al., 1994; Danforth and Cheng, 1995; Pappa et al., 1999; Fowler et al., 2002). A study using human follicular fluid as a source (Pappa et al., 1999) has shown a molecular weight of 12.5 kDa and identity to the C-terminal fragment of human serum albumin (HSA).

That GnSAF may be related to HSA was further supported by two recent studies. In one of them (Tavouliari et al., 2004), the production of recombinant polypeptides of HSA corresponding to subdomain IIIB residues of 490–585 was feasible by using the expression-secretion system of Pichia Pastoris GS115. Different clones were obtained that in the *in vitro* bioassay system of rat pituitary cells were able to reduce the GnRH-induced LH secretion demonstrating, therefore, GnSAF bioactivity (Tavouliari et al., 2004). More recently, with the use of RT-PCR and the appropriate primers, the expression of HSA mRNA was found in human granulosa cells obtained from women undergoing IVF treatment (Karligiotou et al., 2006). All fragments of HSA were expressed in the nucleus of the granulosa cells, and only the promoter and the C-terminal fragment were expressed in the cytoplasm (Karligiotou et al., 2006). Evidence has been provided that GnSAF is different from inhibin, first because it reduces LH rather than FSH secretion (Pappa et al., 1999), second because during the process of purification from human follicular fluid inhibin was removed from the system (Pappa et al., 1999; Fowler et al., 2002) and third because when antibodies against inhibin were used *in vitro* the bioactivity of GnSAF was preserved (Balen et al., 1995a; Byrne et al., 1995).

Several studies have shown *in vivo* bioactivity of GnSAF during ovarian stimulation in women with FSH (Messinis et al., 1991, 1993a,b, 1994, 1996). It has been suggested that FSH stimulates the production of GnSAF from growing follicles but not from the corpus luteum (Messinis et al., 1996).

**Physiological role of GnSAF: LH surge amplitude**

Although GnSAF bioactivity is particularly evident during ovarian stimulation, it is possible that this factor plays a physiological role during the normal menstrual cycle affecting gonadotrophin secretion. Studies in women during the natural cycle have suggested that GnSAF is produced during the luteal-follicular transition under the influence of the intercycle rise of FSH (Messinis et al., 1991, 1993c, 2002) (Figure 3). A hypothesis has been developed that the activity of GnSAF in the circulation is high during the early- and midfollicular phases, and this maintains the pituitary in a state of low responsiveness to GnRH (Messinis and Templeton, 1991; Fowler et al., 2003; Messinis, 2003). However, in the late follicular phase, there is a decline in GnSAF bioactivity that facilitates the

![Figure 3. Activity of gonadotrophin surge-attenuating factor (GnSAF) during the normal menstrual cycle in relation to inhibin A, inhibin B, estradiol (E2) and progesterone (P4) patterns. It is postulated that GnSAF is produced during the luteal-follicular transition under the influence of the intercycle rise of FSH.](https://academic.oup.com/humupd/article-abstract/12/5/557/776661/563)
sensitizing effect of E\textsubscript{2} on the pituitary and the full expression of the midcycle LH surge (Messinis et al., 1994) (Figure 4).

That GnSAF activity is higher in the early- and midfollicular phases than in the late follicular phase is also supported by in vitro studies demonstrating GnSAF activity in human follicular fluid particularly of small- and medium-sized follicles rather than of large follicles (Fowler et al., 1990, 2001). According to this hypothesis, the role of GnSAF in humans is to control the amplitude and not the onset of the LH surge. In fact, an endogenous LH surge occurs invariably as a response to the positive feedback effect of E\textsubscript{2} either in the early- or in midfollicular phases of the normal menstrual cycle, but this surge is attenuated as compared to midcycle (Taylor et al., 1995; Messinis et al., 2001). Therefore, E\textsubscript{2} and GnSAF seem to interact at the pituitary gonadotrophs with the former expressing a sensitizing effect and the latter an antagonistic effect.

Of the other ovarian hormones, progesterone seems also to play a role in the control of the amplitude of the LH surge. Under experimental conditions in normally cycling or in post-menopausal women, exogenous progesterone amplified the LH surge that was induced by the administration of exogenous estrogen (Liu and Yen, 1983; Messinis and Templeton, 1990). Data in rats have shown that progesterone can reduce ER\textsubscript{α} and ER\textsubscript{β} protein and increase a truncated ER product that suppresses the activity of both types of receptors in vivo and in cell lines, suggesting that this may be a mechanism via which these steroids limit the positive feedback effect (Schreihofer et al., 2000, 2002). More recent data, however, have demonstrated that the loss of the LH surges in ovariectomized rats during chronic treatment with E\textsubscript{2} was achieved without any changes in the proportion of GnRH cells expressing ER\textsubscript{α} or ER\textsubscript{β} (Legan and Tsai, 2003).

Serum progesterone levels in women increase gradually from the onset to the end of the LH surge and continuously during the luteal phase of the cycle (Hoff et al., 1983). It is possible that the rising progesterone levels contribute to the termination of the LH surge via a negative feedback effect. Experimental data in women have shown that when an LH surge was induced with the exogenous administration of E\textsubscript{2}, LH values declined following the peak but went down to the presurge level only after the administration of progesterone (Messinis and Templeton, 1990).

**Termination of the LH surge**

The midcycle LH surge normally has a duration of 48–72 h (Hoff et al., 1983; Messinis and Templeton, 1988a; Shoham et al., 1995). The factors, however, that control the termination of the endogenous LH surge during the normal menstrual cycle have not been clarified. After the onset of the LH surge, E\textsubscript{2} concentrations decline. It is rather unlikely that the withdrawal of the E\textsubscript{2} effect terminates gonadotrophin secretion, because termination also occurred in experiments in which high estrogen concentrations were maintained during the LH surge (Liu and Yen, 1983). In addition, animal studies have shown that E\textsubscript{2} is important for triggering the LH surge but is not required after its onset (Evans et al., 1997). Nevertheless, data in rats have shown that estrogen can reduce ER\textsubscript{α} and ER\textsubscript{β} protein and increase a truncated ER product that suppresses the activity of both types of receptors in vivo and in cell lines, suggesting that this may be a mechanism via which these steroids limit the positive feedback effect (Schreihofer et al., 2000, 2002). More recent data, however, have demonstrated that the loss of the LH surges in ovariectomized rats during chronic treatment with E\textsubscript{2} was achieved without any changes in the proportion of GnRH cells expressing ER\textsubscript{α} or ER\textsubscript{β} (Legan and Tsai, 2003).

Serum progesterone levels in women increase gradually from the onset to the end of the LH surge and continuously thereafter, during the luteal phase of the cycle (Hoff et al., 1983). It is possible that the rising progesterone levels contribute to the termination of the LH surge via a negative feedback effect. Experimental data in women have shown that when an LH surge was induced with the exogenous administration of E\textsubscript{2}, LH values declined following the peak but went down to the presurge level only after the administration of progesterone (Messinis and Templeton, 1990).
A recent study has provided more information regarding the mechanism that is responsible for the termination of the endogenous LH surge in women (Dafopoulos et al., 2006). In particular, the positive feedback effect of exogenous E2 was investigated in two cycles of normally cycling women who underwent ovariectomy on day 3 of the second cycle. An endogenous LH surge was induced by exogenous E2 given from cycle days 3–5 that was comparable in the two cycles up to the point of the LH peak. A descending limb, however, was evident only in the first cycle with the intact ovaries. In contrast, in the second cycle in which the ovaries were removed, LH and FSH levels did not decline but fluctuated around the peak value of the surge for the rest of the experimental period (Dafopoulos et al., 2006). These data suggest that the termination of the E2-induced LH surge is not related to an exhaustion of the pituitary reserves but is controlled by ovarian factors. As progesterone values decreased after ovariectomy and were lower than during the corresponding days in the first cycle with the intact ovaries, this steroid is a possible candidate for the surge termination. A decrease in GnRH pulse frequency in the late cycle as compared to the early- and mid-portions of the midcycle LH surge (Adams et al., 1994) can be part of the mechanism of progesterone action on gonadotrophin secretion.

Menopause

Following menopause, changes in the relationships between the ovaries and the hypothalamic-pituitary system take place. Ovarian failure leading to menopause is a gradual process that usually starts several years before menopause (Burger et al., 2002). It has been shown that basal FSH concentrations are raised, whereas those of inhibin B are reduced in the early follicular phase of the cycle during the perimenopausal period, although cyclicity is maintained (Klein et al., 1996; Soules et al., 1998). At the same time, LH values remain normal suggesting that the negative feedback effect of the ovaries is partly attenuated long before menopause. After menopause, however, the negative feedback mechanism is abolished, since following ovariectomy in healthy post-menopausal women FSH, LH, and E2 values do not change and only testosterone levels decline substantially (Dafopoulos et al., 2004b). Therefore, the post-menopausal ovaries do not produce estrogens but only testosterone (Sluijmer et al., 1995; Laughlin et al., 2000) which, however, does not contribute to the negative feedback system (Dafopoulos et al., 2004b). The latter can be re-established in post-menopausal women after the exogenous administration of estrogens and progesterone (Yen and Tsai, 1971b; Lind et al., 1978; Lutjen et al., 1986). Despite the absence of ovarian feedback, age-related changes occur in the hypothalamic component that are characterized by a decrease in GnRH pulse frequency with age (Lambalk et al., 1997; Santoro et al., 1998; Hall et al., 2000).

Due to the very low circulating E2 concentrations in the post-menopausal women, the positive feedback mechanism is also not active. However, the secretion of LH and FSH and, therefore, GnRH is still pulsatile (Hall et al., 2000). Furthermore, in a recent study, the pituitary sensitivity to GnRH, assessed as the 30 min response to 10 μg GnRH i.v., remained unchanged during the week following ovariectomy as compared to the pre-operative pattern (Dafopoulos et al., 2004b). When, however, exogenous estrogens were given to post-menopausal women in order to achieve concentrations similar to those during the follicular phase of the normal menstrual cycle, the sensitivity of the pituitary to GnRH increased gradually (Dafopoulos et al., 2004a). Also, a LH surge can be induced in post-menopausal women after the exogenous administration of estrogens (Tsai and Yen, 1971; Lachelin and Yen, 1978; Liu and Yen, 1983; Lutjen et al., 1986). It is clear, therefore, that after menopause the absence of the feedback mechanisms is due to ovarian insufficiency, whereas the hypothalamic-pituitary system remains intact with increased GnRH secretion and able to respond to the negative and positive feedback effects of exogenous steroids (Gill et al., 2002). Nevertheless, because the magnitude of the response in post-menopausal women has not been quantified in a comparative way with that in premenopausal women, an altered sensitivity to the ovarian steroids cannot be excluded, based on recent data in perimenopausal women suggesting hypothalamic-pituitary insensitivity to estrogens (Weiss et al., 2004).

Clinical implications

Abnormal conditions

During the reproductive years, disturbances in the feedback mechanisms may occur, characterized by menstrual irregularities, such as dysfunctional uterine bleeding, menorrhagia or amenorrhea. In terms of the negative feedback mechanism, a possible abnormality is a reduced suppression of gonadotrophin secretion. This happens when the production of ovarian steroids is inadequate as in primary ovarian failure or after ovariectomy. Women with premature ovarian failure and ovulatory cycles have higher FSH and lower inhibin B and inhibin A levels (Welt et al., 2005a). Although premature ovarian failure is a permanent condition, in some cases the ovaries become only temporarily inactive. When, however, gonadotrophin levels decrease either spontaneously or after treatment with E2, normal cyclicity is re-established and even a pregnancy can occur (Taylor et al., 1996).

The opposite situation, i.e. an augmented negative feedback mechanism has not been described in humans. It is known that in women with PCOS serum FSH is normal, while LH is either normal or elevated (Balen et al., 1995b). The inability of follicles to mature to the preovulatory stage in these patients is due at least in part to the lack of an intercycle rise of FSH, as when FSH concentrations are slightly elevated by the exogenous administration of this hormone, follicle selection can take place (van der Meer et al., 1994). Although the pathophysiology of this syndrome is in several aspects unclear, the lack of an intercycle rise of FSH may be partly related to an augmentation of the negative feedback effect mediated by elevated inhibin. It has been shown, however, that inhibin levels are not higher in patients with PCOS as compared to controls (Pigny et al., 2000). On the contrary, the concentrations of both inhibin A and inhibin B in the follicular fluid of PCOS follicles have been found to be significantly lower than in size-matched follicles from normal women (Welt et al., 2005b).

Normally cycling women express a positive feedback effect at midcycle and ovulate invariably. In cases of follicle arrest including hyperandrogenic conditions, PCOS, hyperprolactinaemia, hypogonadotrophic-hypogonadism and premature ovarian failure, there is no regular expression of a positive effect of endogenous E2. With the exception of hypogonadotrophic-hypogonadism, in
the majority of these cases, a positive feedback effect can be demonstrated during an estrogen provocation test (Shaw, 1976). Therefore, when ovulation is induced in hypogonadotrophic-hypogonadal women, hCG should be given to induce final follicle maturation (Messinis, 2005). It has been suggested that the elevated LH that is seen in the serum of about 40% of patients with PCOS is related to a continuous positive action of E2 on the pituitary (Lobo et al., 1981; Waldstreicher et al., 1988). Although this has to be confirmed, such an action does not fulfil the criteria of a positive feedback effect. However, a continuous sensitizing action of E2 on the pituitary that enhances the pituitary response to GnRH in PCOS patients cannot be excluded, although data in monkeys do not support such a hypothesis (Richardson et al., 1992).

**Administration of pharmaceutical compounds**

Changes in the integrity of the feedback system can occur in normal women under the treatment with various pharmaceutical compounds. Oral contraceptives, containing ethinylestradiol and a progestagen, maintain the pituitary in a state of low secretion of gonadotrophins. During the week free of treatment, a FSH rise is usually below the threshold for follicle selection, and due to follicle arrest, an endogenous LH surge does not occur (Kuhl et al., 1985). Administration of E2 to normal women during the second half of the luteal phase reduces FSH intercycle levels and the size of antral follicles (Fanchin et al., 2003a). This results in a better synchronization of follicle growth during the ensuing follicular phase under the stimulation by exogenous FSH (Fanchin et al., 2003b).

Selective blockage of the positive feedback mechanism can be achieved in women with the injection of a GnRH antagonist. When such a compound is given in mid follicular or late follicular phases of the cycle, the endogenous LH surge is blocked or becomes abortive (Leroy et al., 1994). The use, however, of GnRH antagonists as contraceptive means is not feasible due to variability in the time of LH surge onset, as well as the high cost and the inconvenience caused to patients. The GnRH agonists act in a different way than the antagonists and block both the negative and the positive feedback mechanisms (Fraser, 1988). Other drugs that can directly affect the feedback system are the anti-estrogenic compounds, such as clomiphene citrate and tamoxifene. These drugs bind the estrogen receptors and block the negative feedback effect, resulting in increased gonadotrophin secretion (Shaw, 1976). Clomiphene also blocks the positive feedback effect during its administration and for some days after the end of the treatment, while follicle maturation is progressing (Messinis and Templeton, 1988b). An attenuation of the negative feedback effect in women can be also achieved with the use of aromatase inhibitors (Mitwall and Casper, 2001).

Changes in the feedback mechanisms in women can also occur as a result of increased ovarian activity that takes place during ovarian stimulation for IVF. In these cases, the negative feedback is augmented and the positive feedback action is markedly attenuated. During ovarian stimulation, the concentrations of E2 in the circulation become supraphysiological (Messinis et al., 1985), while inhibin concentrations also increase excessively (Tsonis et al., 1988). These result in a significant suppression of LH and FSH secretion (Messinis and Templeton, 1987a; Messinis et al., 1998). Gonadotropin secretion is also markedly reduced during the endogenous LH surge despite the very high E2 concentrations (Messinis et al., 1985). This has been related to the increased production of GnSAF by the stimulated ovaries, which antagonizes the stimulating effect of E2 on the pituitary (Messinis and Templeton, 1989).

Nevertheless, during multiple follicular development, the endogenous LH surge is blocked on several occasions (Messinis and Templeton, 1987a). When a LH surge occurs, it is either premature or on time in relation to the size of the preovulatory follicle (Messinis and Templeton, 1986; Templeton et al., 1986). In clinical terms, a premature LH surge may result in premature luteinization and therefore in a low success rate during IVF treatment. The LH surge in these cases can be prevented by the administration of GnRH analogues, although with the antagonists premature LH peaks >10 IU/l have been reported in a rate from 3 to 35% of the cycles (Albano et al., 2000; Borm and Mannenerts, 2000; Felberbaum et al., 2000; European and Middle East Orgalutran Study Group, 2001; Engel et al., 2002; Messinis et al., 2005). Luteinization, however, occurs in a small percentage of the cases with raised LH.

The importance of LH suppression during ovarian stimulation induction has not been clarified because data in the literature are conflicting (Westergaard et al., 2000; Humaidan et al., 2002; Kolibianakis et al., 2004; Huirme et al., 2005). LH secretion is also suppressed during the luteal phase of stimulated cycles (Messinis and Templeton, 1987b; Tavaniotou et al., 2001). It seems that the suppression of gonadotrophin secretion during ovarian stimulation is a continuous process starting in the follicular phase and ending up in a disrupted luteal phase. The latter is inadequate not only after an attenuated LH surge (Messinis and Templeton, 1987b) but also after hCG, recombinant LH or a GnRH agonist administration for final follicle maturation (Beckers et al., 2003).

**Conclusions**

The two feedback mechanisms are important determinants of the relationships between the ovaries and the hypothalamic-pituitary system. The ovarian steroids, E2 and progesterone, are the principal mediators of the suppressing effect on gonadotrophin secretion during the normal menstrual cycle. Evidence has been provided that for FSH secretion non-steroidal substances, such as inhibin A and B, also play an important role. E2 is the main component of the positive feedback mechanism that induces the mid-cycle endogenous LH surge. Further research is required to clarify the specific role of each of the steroidal and non-steroidal substances in the context of the feedback mechanisms.

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Ovarian feedback mechanisms


Ovarian feedback mechanisms


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