

Endocrine bases of lactational anoestrus in the sow

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Summary — Parturition in the sow is followed by a period of anovulation which is prolonged by lactation. Follicular development and luteinizing hormone (LH) secretion are depressed during the last month of pregnancy. After parturition, LH secretion increases but is again inhibited by the establishment of lactation. Lactating sows are submitted to stimuli originating from the young, whose intensity culminates 3–14 d post-partum (pp), and to high nutrient requirements for milk production. The inhibitory effects of sucklings are imposed during the first 3 d pp and seem to be mediated by the action of opioids at the hypothalamic level. The nutritional deficit constitutes an additional inhibitory factor. As lactation continues, LH secretion progressively increases. A further rise in LH occurs at weaning. Variations in follicle-stimulating hormone (FSH) profiles are less marked. The divergence observed between LH and FSH might be explained by different mechanisms of control; FSH secretion depends mainly on ovarian inhibition whereas LH secretion depends mainly on factors related to lactation. Folliculogenesis progressively resumes during lactation and follicles acquire the ability to respond to the weaning-associated stimuli and begin preovulatory growth. Hormones modified by lactation, such as prolactin, insulin, growth hormone and insulin-like growth factor I, may influence folliculogenesis directly at the ovarian level or *via* modifications of gonadotrophin secretions. In conclusion, the inhibition of the hypothalamo–pituitary–ovarian axis during lactation is mainly due to suckling-induced neuroendocrine reflexes. We hypothesize that the nutritional deficit becomes relatively more important during the third and fourth weeks pp.

lactational anoestrus / suckling / endocrinology / ovarian activity / sow

Résumé — **L'anoestrus de lactation chez la truie.** *Chez la truie, une période sans ovulation suit la parturition. Sa durée est prolongée par la lactation. La croissance folliculaire et la sécrétion de LH sont réduites pendant le dernier mois de la gestation. Après la parturition, la sécrétion de LH augmente mais est à nouveau inhibée par l'établissement de la lactation. Les truies en lactation sont soumises aux stimuli émanant des porcelets, d'intensité maximale entre le 3^e et le 14^e jour post-partum (pp) et aux besoins en nutriments pour la production du lait. L'effet inhibiteur des tétées se met en place dans les 3 premiers jours post-partum. Il semble passer par l'action des opiacés sur la libération de GnRH. Au cours du déroulement de la lactation, la sécrétion de LH augmente progressivement. Un nouvel accroissement de la sécrétion de LH a lieu après le sevrage. Les variations des concentrations de FSH sont moins nettes. Cette différence entre LH et FSH s'expliquerait par des mécanismes de régulation divergents, la sécrétion de FSH étant sous contrôle ovarien et celle de LH dépendante de la lactation. La folliculogenèse se rétablit progressivement pendant la lactation et les follicules deviennent aptes à répondre aux stimuli associés au sevrage pour entamer une croissance préovulatoire. Les hormones*

lactogènes dont les niveaux de sécrétion sont modifiés par la lactation (prolactine, insuline, hormone de croissance, IGF-I) sont susceptibles de moduler la croissance folliculaire par une action directe au niveau ovarien ou par un effet sur la sécrétion gonadotrope. En conclusion, l'inhibition de l'axe hypothalamus-hypophyse-gonades est principalement due aux réflexes neuroendocriniens liés à la tétée. Nous suggérons que l'importance relative du déficit nutritionnel s'accroît pendant les 3^e et 4^e semaines de lactation.

ancestrus de lactation / allaitement / endocrinologie / activité ovarienne / truie

INTRODUCTION

In numerous mammalian species, parturition is followed by a period of anovulation of variable duration. Lactation is one of the main regulators with a strong inhibitory influence on the occurrence of oestrus and/or ovulation. The effects of lactation are mainly due to the stimuli originating from teat stimulation but also to the metabolic adaptations necessary for milk production.

In domestic sows living in a semi-natural environment, the weaning of the young is a slow and gradual process with the final sucklings occurring between 13 and 18 weeks post-partum (pp) (Jensen and Recén, 1989). In commercial piggeries, lactation is interrupted at 3–5 weeks pp, around the time of the peak of milk production. In this situation, sows are usually in anoestrus during lactation, and a fertile oestrus is observed within 10 d after weaning in most of the sows (Aumaitre *et al*, 1976; Maurer *et al*, 1985). However, in a variable proportion of females, oestrus is delayed, and the weaning-to-oestrus interval is an important component of herd productivity. This interval should be minimized in order to optimize the efficiency and profitability of the enterprise.

The aim of this paper is to review the existing knowledge of the endocrine mechanisms involved in lactational anoestrus in the sow. Long-term effects of gestation, farrowing and return to oestrus after farrowing will be briefly presented. Information on the activity of the hypothalamo-pitu-

itary-ovarian axis during lactation and after weaning will be reviewed more extensively.

LONG-TERM EFFECTS OF GESTATION AND FARROWING

Activity of the hypothalamo-pituitary-ovarian axis during gestation and farrowing

High concentrations of progesterone are necessary for the maintenance of pregnancy. This hormone is essentially secreted during gestation by the corpora lutea in the pig (Nara *et al*, 1981). Circulating concentrations of progesterone remain high for approximately 3 months and decline during the last week of pregnancy (Robertson and King, 1974) (fig 1). This decrease is due to the regression of the corpora lutea which become completely inactive 2 or 3 d after parturition.

A transient rise in oestrogen secretion occurs early in pregnancy (Fèvre *et al*, 1968; Robertson and King, 1974). Thereafter, plasma oestrogen concentrations increase in a curvilinear manner from day 70 until parturition (fig 1). In fact, both non-conjugated oestrogens, oestrone, oestradiol-17 β , and conjugated oestrogens increase in early and late gestation (Terqui, 1978). These circulating oestrogens are mainly of foeto-placental origin (Fèvre *et al*, 1968). In late pregnancy, corticosteroid concentrations increase and are maximal around farrowing (Baldwin and Stabenfeld, 1975).

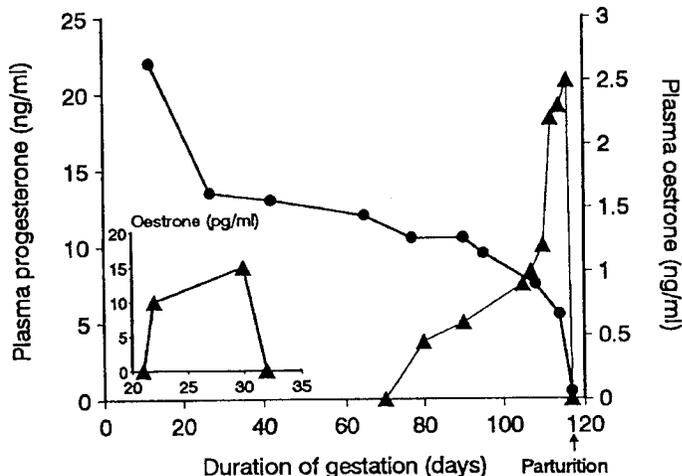


Fig 1. Profiles of plasma progesterone (●) and oestrone (▲) in sows throughout gestation (redrawn from Robertson and King, 1974). The inset shows the transient rise in oestrogen plasma concentrations (▲) in early pregnancy.

The concentrations of plasma LH fluctuate in an episodic and pulsatile manner throughout pregnancy (Ziecik *et al*, 1982/1983; Kraeling *et al*, 1992). The levels of LH in early and mid-pregnancy are similar to those observed in the mid-luteal phase of the oestrous cycle (Ziecik *et al*, 1982/1983). The number of LH pulses does not vary between 30 and 70 d of gestation, whereas it decreases between 70 and 90 d of gestation and remains low thereafter (Parvizi *et al*, 1976; Kraeling *et al*, 1992). In miniature pigs, ovariectomy during the follicular phase, and ovariectomy on day 100 of pregnancy followed by abortion, result in a similar increase in LH secretion (Parvizi *et al*, 1976). Taken together, these results strongly suggest that high concentrations of progesterone inhibit LH pulsatility throughout pregnancy and that high concentrations of oestrogens amplify this inhibition during the last month of pregnancy. This is in agreement with the known negative feedback actions exerted by oestradiol and progesterone on gonadotrophin release in domestic mammals (Goodman and Karsch, 1980).

The circulating concentrations of prolactin remain low during the majority of ges-

tation and rise during the last week (Dusza and Krzymowska, 1981; Kraeling *et al*, 1992). They reach maximum levels at the time of delivery (Dusza and Krzymowska, 1981).

Few data are available concerning folliculogenesis in the pregnant sow. Small (1–4 mm in diameter) and large follicles (4–6 mm in diameter) are present in the ovaries throughout pregnancy (Rexroad and Casida, 1975; Wiesak *et al*, 1992). The number of large follicles increases during the first 2 months of pregnancy and declines thereafter, whereas the number of small follicles tends to increase (Rexroad and Casida, 1975). No spontaneous ovulation occurs during gestation. However, it is possible to induce ovulation and obtain functional corpora lutea by exogenous gonadotrophins throughout gestation (du Mesnil du Buisson, 1973).

In summary, LH secretion and follicular development are inhibited during the last month of gestation compared with the luteal phase and early and mid-gestation. Progesterone is probably the main inhibitory factor. However, as the increase in oestrogen secretion by the foeto-placental units

in late gestation parallels the inhibition of the hypothalamo–pituitary–ovarian axis, oestrogens may contribute to this inhibition.

Long-term effects of gestation and farrowing on post-partum ovulation

Weaning piglets at birth, instead of at 3–7 weeks of age, results in a longer weaning-to-oestrus interval (between 8 and 16 d), a longer farrowing-to-remating interval (Elliot *et al*, 1980) and a high incidence of cystic follicles (Peters *et al*, 1969). Thus, it seems that physiological events associated with gestation and parturition have an inhibitory influence on pp ovulation.

In cyclic gilts, the occurrence of cystic follicles has been related to a lack of the preovulatory LH surge, which itself could be due to high corticosteroid levels (see review by Ryan and Raeside, 1991). Such a hypothesis could apply to sows weaned at farrowing (zero-weaned sows), since glucocorticoids are elevated in females that have undergone premature weaning (Ryan and Raeside, 1991). A dysfunction in the oestrogen-induced positive feedback in lactating sows shortly after farrowing (until 14–16 days pp) has also been described (Elsaesser and Parvizi, 1980; Cox *et al*, 1988; Sesti and Britt, 1993). Such a phenomenon may involve the long-term influence of gestation and parturition on the hypothalamo–pituitary unit. However, no data are available in zero-weaned sows.

Uterine involution could also play a role in the long-term effects of pregnancy. In lactating sows, uterine involution is achieved within 21–28 d pp (Palmer *et al*, 1965a,b). To our knowledge, no data are available on the interaction between uterine involution and ovarian activity in the pig species.

Thus, gestation and farrowing have inhibitory consequences on ovarian activity between farrowing to about day 16 pp.

EFFECTS OF NURSING AND MILK PRODUCTION

In pigs, the effects of nursing and milk production cannot be dissociated, since lactation is not maintained without suckling by the young. Lactating sows are receiving physical and behavioural stimuli from the piglets and have high nutrient requirements for milk production (fig 2). Stimulation of the teats stimulates the release of neuropeptides and hormones through neuroendocrine reflexes. Nursing and milk production are highly dependent since milk synthesis ceases and mammary alveolar cells degenerate if milk is not removed (Baldwin and Plucinski, 1977).

Metabolic needs for milk production as well as stimuli originating from the piglets have consequences on circulating levels of nutrients, and on the release of neurotransmitters and numerous hormones, which would themselves influence the activity of the hypothalamo–pituitary–ovarian axis (see reviews by Varley and Foxcroft, 1990; I'Anson *et al*, 1991). We will examine the consequences of lactation on reproductive activity and attempt to separate inhibitory effects due to suckling *per se* from the metabolic consequences of lactation.

Main physiological events associated with lactation

Suckling behaviour

The frequency of suckling is high during the first 2 d of lactation (around 6 sucklings per hour during the first 6 h following parturition, De Passillé, 1982). It declines very quickly and remains nearly unchanged at approximately 1 suckling per hour, from day 3 pp until 10 weeks pp (Salmon Legagneur, 1956; Jensen and Recén, 1989). By the end of day 3, piglets massage the udder prior to and after milk let-down (Gill and Thomson,

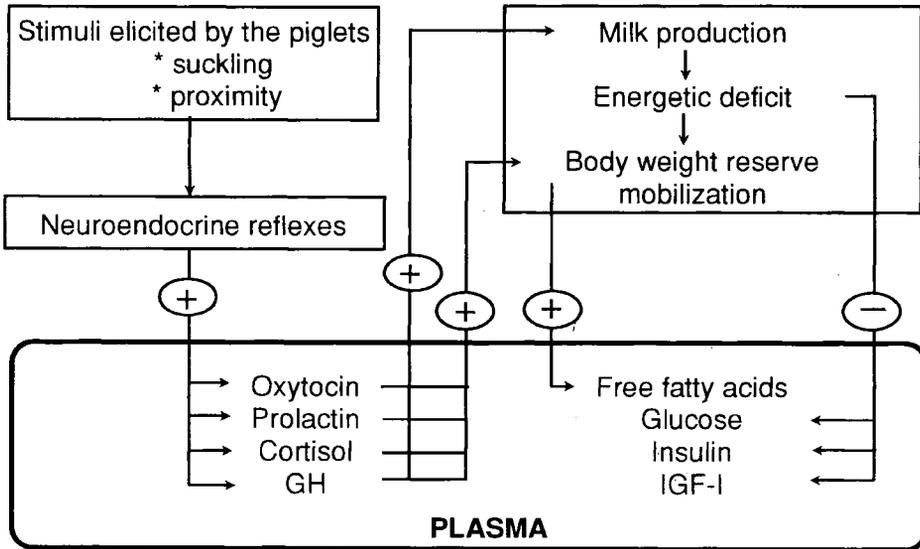


Fig 2. Schematic representation of neuroendocrine and metabolic consequences of suckling and milk production.

1956; De Passillé, 1982; Jensen and Recén, 1989). The average duration of the final massage decreases from about 3–4 to 1–2 min between the first and third week of lactation (Gill and Thomson, 1956; Jensen and Recén, 1989).

Energetic balance and circulating metabolites

The energetic balance of lactating sows is the difference between nutrient intake and nutrient requirements for maintenance and milk production. Maintenance requirements depend essentially on body weight and, to a lesser extent, on ambient temperature. They show little variation during lactation. Energy requirements for milk production increase during the first 3 weeks of lactation (Salmon Legagneur, 1956; Noblet and Etienne, 1986). They are mainly influenced by the litter size. Except during the first days following farrowing, sows are fed *ad libitum* or

close to *ad libitum*. Their voluntary feed intake increases progressively during the first 3 weeks of lactation and depends on numerous endogenous and environmental factors (see review by Dourmad, 1988). In sows producing an amount of milk satisfactory for piglet growth (at least 200 g/piglet/d), the energetic balance is negative throughout lactation and becomes positive after weaning (fig 3).

Preprandial concentrations of glucose are lower in lactating sows compared with weaned sows, whereas those of free fatty acids are enhanced (Armstrong *et al*, 1986a; Prunier *et al*, 1993). However immediately after a meal, plasma concentrations of glucose increase and free fatty acids decrease in both types of females (Prunier and Guingand, unpublished data; fig 4). The average concentrations of glucose decrease from the first week of lactation to the fourth week pp (Tokach *et al*, 1992a; Prunier *et al*, 1993). This variations is consistent with the observation that the mammary gland

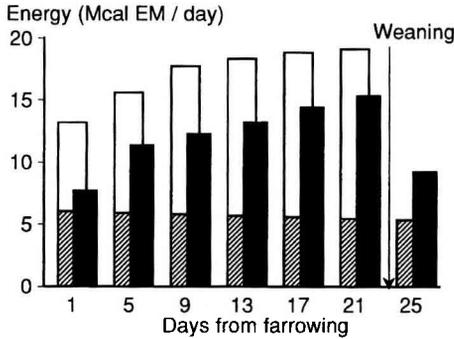


Fig 3. Daily requirements and input of metabolizable energy (kcal/day) during lactation and after weaning for a 'medium' productive primiparous sow (data are calculated from Noblet and Etienne, 1986, and Dourmad, 1991). Maintenance (hatched); milk (white); and feed intake (black).

utilizes about 50% of the plasma glucose available (Spencer *et al*, 1969) and that energy output in milk increases between the first and fourth weeks of lactation (Noblet and Etienne, 1986). High concentrations of free fatty acids and glycerol are the signs of body fat mobilization, whose intensity depends mainly on food intake and milk output. Free fatty acids are susceptible to increase throughout lactation and this variation depends on the nutritional balance of sows (Weldon *et al*, 1994). After weaning, mean free fatty acid and glycerol concentrations decrease during the first weeks (Clowes *et al*, 1994).

Collectively, these results show that during lactation plasma glucose is low as a consequence of high mammary utilization, whilst free fatty acids are elevated since the sow must mobilize body reserves to meet the nutrient requirements of milk production.

Peptidergic neurotransmitters

It has been proposed that in the rat several neurotransmitters, including serotonin,

dopamine and opioids, are influenced by suckling and mediate its effects within the hypothalamus. In lactating sows, the results of numerous experiments using naloxone to block the action of endogenous opioids strongly suggest their release during suckling (Varley and Foxcroft, 1990). The release and effects of the peptidergic neurotransmitters, dopamine and serotonin, during suckling, has received little attention in sows until now. In addition to suckling, the catabolic state associated with lactation may also influence the release of neurotransmitters, such as catecholamines, serotonin and opioids (l'Anson *et al*, 1991). However, evidence for such effects are again lacking in the sow.

Variations in lactogenic hormones

Around parturition, there is a massive, transient release of the posterior pituitary hormone oxytocin (fig 2) (Forsling *et al*, 1979). During lactation, udder stimulation induces immediate and short-lasting peaks of oxytocin (Forsling *et al*, 1979; Kendall *et al*, 1983; Uvnäs-Moberg *et al*, 1985), which stimulate milk ejection. The amplitude and frequency of the oxytocin peaks decline around the third week of lactation in miniature sows (Forsling *et al*, 1979).

Concentrations of prolactin in plasma are elevated around parturition (Dusza and Krzymowska, 1981). They decline sharply immediately after parturition (Dusza and Krzymowska, 1981), and then gradually decrease as lactation progresses, but remain much higher than during the oestrous cycle (Bever *et al*, 1978; Stevenson *et al*, 1981; Edwards and Foxcroft, 1983a). At weaning, prolactin concentrations fall abruptly and are low 4–6 h later (Bever *et al*, 1978; Stevenson *et al*, 1981; Edwards and Foxcroft, 1983a).

During lactation, suckling by piglets elicits an increase in prolactin (Kendall *et al*, 1983; Mattioli *et al*, 1988; Algers *et al*, 1991).

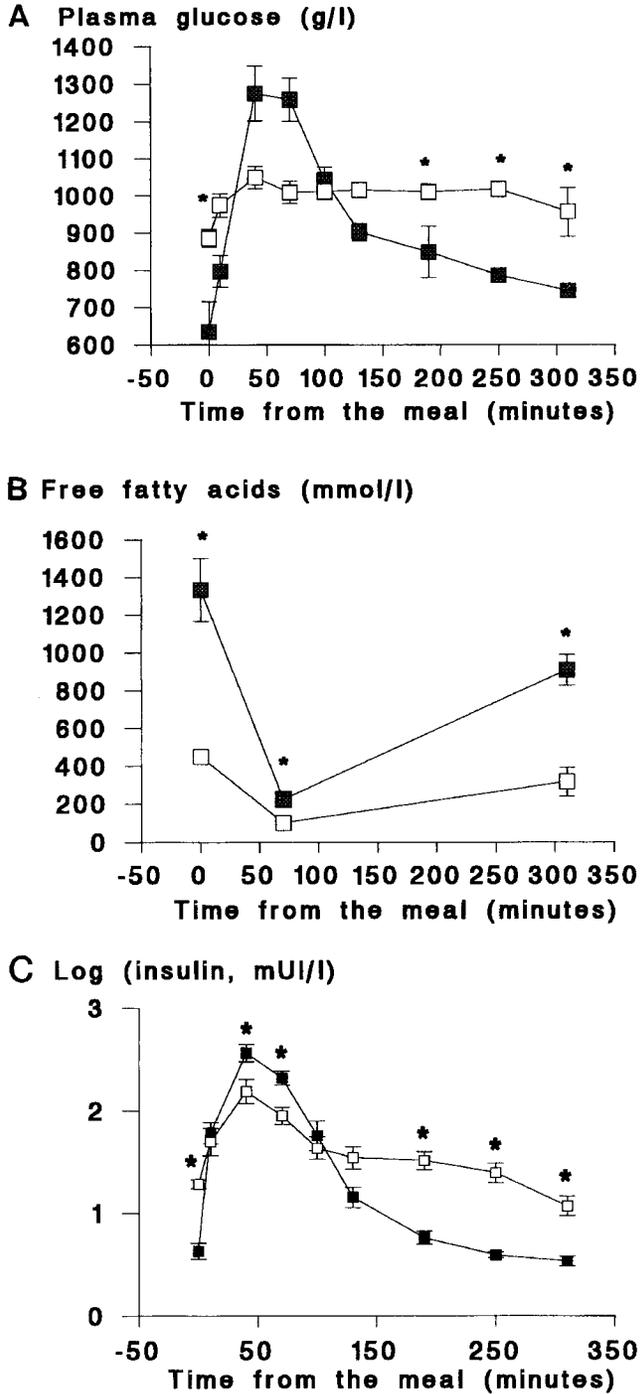


Fig 4. Plasma levels of glucose (A), free fatty acids (B) and insulin (C) after a meal (1 kg of a standard diet for lactating sows), before weaning (BW ■) and after weaning (PW □) in 10 primiparous sows (Prunier and Guingand, unpublished data). * Values are significantly different ($P < 0.05$).

This effect of suckling is mediated, at least in part, through an opioid-dependent mechanism (Mattioli *et al*, 1986; Barb *et al*, 1987; Armstrong *et al*, 1988a). A quantitative relationship between the release of prolactin and the duration of udder stimulation has been observed by Algers *et al* (1991). Thus, during lactation, the decrease in the duration of udder massage could explain the decline in prolactin concentration.

Concentrations of growth hormone (GH) are elevated around parturition (De Hoff *et al*, 1986). During lactation, mean plasma concentrations of GH are high with frequent spikes (Schams *et al*, 1994). As for prolactin, suckling by piglets induces an increase in GH concentrations, which is mediated, at least in part, by an opioid-dependent mechanism (Armstrong *et al*, 1990; Rushen *et al*, 1993). Moreover, GH secretion may be increased by negative energetic balance, through a decrease in insulin and insulin-like growth factor-I (IGF-I) levels, as shown in other species (see review by Phillips, 1986).

Preprandial insulin concentrations are low during lactation (Eriksson *et al*, 1987; Prunier *et al*, 1993). After a meal, the peak of insulin is of similar amplitude in lactating and weaned sows, but the decrease is more rapid and steeper in lactating sows (Prunier and Guingand, unpublished data) (fig 4). The average concentrations of insulin over several hours are lower before than after weaning (Rojkittikhun *et al*, 1992). During lactation, mean and preprandial insulin declines between the first and fourth weeks pp (Tokach *et al*, 1992a; Weldon *et al*, 1994). A weak positive correlation has been observed between the release of insulin and the intensity of the teat massage performed by the piglets before milk let-down (Algers *et al*, 1991). The basis and physiological significance of this phenomenon are unknown. Overall, variations of insulin follow those of glucose. Low concentrations of insulin during lactation probably contribute to a preferential drive of glucose and amino acids

towards the mammary glands since insulin promotes the utilization of these nutrients by peripheral tissues.

IGF-I is elevated around parturition and decreases thereafter (Simmen *et al*, 1988). Few data are available during lactation and around weaning. Schams *et al* (1994) observed high concentrations of plasma IGF-I during lactation, which did not decline significantly after weaning. There is no information on the nutritional balance of the sows from this experiment. In animals with a negative nitrogen and/or energetic balance, plasma IGF-I concentrations are reduced (l'Anson *et al*, 1991). Low concentrations of circulating IGF-I, associated with hypoinsulinaemia might favour lipolysis and constitute an adaptative mechanism that facilitates fatty acid availability to the mammary glands (l'Anson *et al*, 1991). In the days following weaning, IGF-I concentrations do not vary (Clowes *et al*, 1994).

Variations in the gonadotrophic axis during lactation and around weaning

Secretory patterns of GnRH and gonadotrophins

Hypothalamic concentrations of GnRH are low during lactation and increase after weaning (Cox and Britt, 1982a). In lactating sows, the pituitary content of FSH is high, whereas that of LH is low (Crighton and Lamming, 1969). After weaning, pituitary content of LH increases in contrast to that of FSH which does not change (Crighton and Lamming, 1969; Cox and Britt, 1982a).

Mean concentrations of circulating LH are high during the 3 d following parturition and decrease thereafter (Tokach *et al*, 1992a; De Rensis *et al*, 1993a,b). Serial profiles show short-term variations in LH concentrations similar to those described during the late follicular phase in cyclic gilts (De Rensis *et al*, 1993a). Pulses are not clear cut and, in one paper, the authors could not identify any pulse on the day of

farrowing (Tokach *et al*, 1992a). The comparison between lactating sows and sows weaned immediately after farrowing (zero-weaned) shows that the mean level and pulsatility of LH are similar in both groups at day 1 pp, and become higher in zero-weaned sows as soon as day 4 pp (Smith *et al*, 1992; De Rensis *et al*, 1993a). Mean concentrations of circulating LH and number of LH pulses are low during early lactation, from about days 4 to 14, and gradually increase thereafter (Stevenson *et al*, 1981; Shaw and Foxcroft, 1985; De Rensis *et al*, 1993b). Weaning between 3 and 5 weeks pp results in an immediate and transient increase in LH mean levels and pulsatility (Parvizi *et al*, 1976; Van de Wiel *et al*, 1978; Shaw and Foxcroft, 1985; Armstrong *et al*, 1986b). From these results, we conclude that (i) the decline in progesterone and oestrogen concentrations at farrowing is probably the main cause of the transient increase in LH secretion immediately after parturition; and (ii) suckling has an inhibitory influence on LH secretion which develops during the first days of lactation and starts to decline around the third week.

There are fewer data concerning the variation in FSH secretion during lactation. Within the 3 d of parturition, FSH concentrations do not vary with time and are similar in suckled and zero-weaned sows (De Rensis *et al*, 1993a). In both types of females, high variability is observed between individuals. From the second week of lactation onwards, a continuous increase in plasma FSH has been observed by Stevenson *et al* (1981) and De Rensis *et al* (1993b). In Large White sows, Prunier and Guingand (unpublished data) did not observe a significant trend in FSH levels between days 14 and 26 pp. Around weaning, some authors have observed no significant change in FSH (Stevenson *et al*, 1981; Edwards and Foxcroft, 1983a; Foxcroft *et al*, 1987), whereas others have reported that FSH concentrations rise after weaning (Cox and Britt, 1982a; Shaw and

Foxcroft, 1985). In fact, individual profiles of plasma FSH differ considerably between sows with a significant increase immediately after weaning in some animals and no variation in others (Foxcroft *et al*, 1987; Prunier and Guingand, unpublished data).

Ovarian activity

Ovarian activity during lactation and around weaning in the pig has received little attention. It has been established that folliculogenesis is still active during lactation, although follicles do not reach the ovulatory size (≥ 6 mm) (Palmer *et al*, 1965a; Crighton and Lamming, 1969; Kunavongkrit *et al*, 1982; Rojanasthien *et al*, 1987a). The size of the largest ovarian follicles increases as lactation progresses, with a concomitant decline in the number of small follicles and in the percentage of atretic follicles (Palmer *et al*, 1965a; Kunavongkrit *et al*, 1982) (fig 5). This is probably the consequence of enhanced gonadotrophin secretion. The reasons why follicles do not reach the pre-ovulatory size during lactation are not fully known. It could be due to insufficient gonadotrophin stimulation and/or to other factors acting directly at the ovarian level (discussed below).

Progesterone concentrations in peripheral blood remain low during lactation, in accordance with the absence of active corpora lutea (Stevenson *et al*, 1981). Most data suggest that circulating oestrogens are low and do not show any time-related variation throughout lactation (Baldwin and Stabenfeldt, 1975; Stevenson *et al*, 1981; Kirkwood *et al*, 1984a; Prunier *et al*, 1993). The oestrogens that can be measured may be of extra-ovarian origin, such as body fat or adrenal cortex, because ovariectomy has no influence on their concentrations (Stevenson *et al*, 1981).

Immediately after weaning, the number and size of large follicles (diameter ≥ 5 mm) increase (fig 5) (Palmer *et al*, 1965a; Crighton and Lamming, 1969; Cox and Britt,

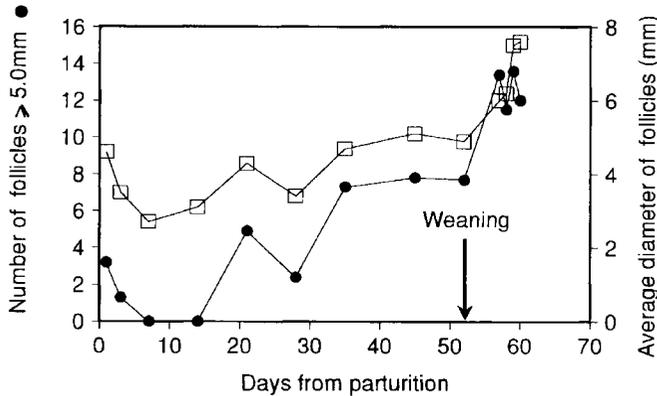


Fig 5. Follicular populations during lactation and after weaning drawn from Palmer *et al*, 1965a.

1982a; Armstrong *et al*, 1986b). This stimulation of follicular growth is accompanied by modifications in follicular function. A transient rise in follicular fluid concentration of progesterone is observed 6–12 h after weaning, whereas oestradiol-17 β concentrations increase gradually and continuously from 6 h after weaning (Killen *et al*, 1992). In sows with a normal return to oestrus, plasma oestradiol-17 β rises significantly within 24–48 h after weaning (Rojanasthien, 1988; Prunier *et al*, 1994). In follicular fluids, relatively high concentrations of oestradiol-17 β and testosterone are present 48 h after weaning (Foxcroft *et al*, 1987). Concentrations of inhibin in plasma and follicular fluids rise progressively during the first 2 d following weaning (Trout *et al*, 1992).

Inhibitory mechanisms of lactation on the reproductive function

GnRH pulsatility and opioid-related inhibition

The reduced secretion of gonadotrophins during lactation is probably related to the low secretion of hypothalamic GnRH, and possibly to a decreased pituitary sensitivity to this neuropeptide. These hypotheses have been partly investigated and the

results suggest that both hypotheses are valid. The inhibition of LH pulsatility in lactating sows suggests a blockade of the GnRH pulsatility.

Transient removal of the piglets for 6 or 8 h results in a concurrent increase in LH pulsatility (Mattioli *et al*, 1988; Armstrong *et al*, 1988a,b). Prevention of suckling with piglets remaining in the vicinity of the sow, induces less marked changes in LH and prolactin concentrations than complete removal of the piglets (Mattioli *et al*, 1988). It was therefore proposed that, even if udder stimulation is the major stimulus involved in the inhibition of LH during lactation, other stimuli originating from the piglets, such as grunting or odor, may be of some importance. There is now evidence that this suckling-related suppression of LH secretion is, at least in part, mediated by endogenous opioid peptides acting at the hypothalamic level. During most of the lactation, but not after weaning, injection of naloxone (an opioid antagonist) induces an increase in LH concentrations (Barb *et al*, 1986; Mattioli *et al*, 1986). Infusion of naloxone results in a higher frequency of LH pulses as soon as day 10 pp (Armstrong *et al*, 1988a; De Rensis *et al*, 1993b). In contrast, administration of morphine, an agonist of endogenous opioids, prevents the rise in LH induced by transient removal of the litter

(Armstrong *et al*, 1988b). Endogenous opioids probably act within the pig hypothalamus to reduce GnRH release and thereby inhibit LH secretion. However, in early lactation (42–78 h pp), administration of naloxone has no influence on LH secretion (De Rensis *et al*, 1993b). This is consistent with the observation that LH secretion is independent of suckling status at this early stage of lactation. During the second and third weeks of lactation, the decrease in udder massage after milk let-down could result in a lower stimulation of opioidergic neurons and might explain the increase in LH secretion.

The influence of endogenous opioids on FSH secretion in lactating sows has been poorly studied and the results are contradictory. Barb *et al* (1987) observed that naloxone treatment increased FSH secretion in lactating sows, whereas De Rensis *et al* (1993b) did not find any effect.

Ovarian negative feedback

Ovariectomy results in an increase in basal and GnRH-stimulated FSH secretion in lactating sows (Stevenson *et al*, 1981). Using the technique of follicle electrocautery, Cox *et al* (1987a) have confirmed that FSH secretion during lactation is dependent upon ovarian inhibition. Treatment with an oestradiol-17 β implant has no effect on FSH levels in intact lactating females (De Rensis *et al*, 1991). These experiments suggest that FSH secretion during lactation is, at least in part, under the control of an ovarian non-oestrogenic inhibitory factor, which is probably inhibin.

In contrast, ovariectomy has no effect on pituitary LH content (Crighton and Laming, 1969) or on basal or GnRH-induced secretion of LH in lactating sows (Parvizi *et al*, 1976; Stevenson *et al*, 1981). Therefore, the inhibition of LH secretion during lactation is not dependent on ovarian feedback. However, LH secretion is sensitive

to the negative feedback action of exogenous oestradiol (De Rensis *et al*, 1991), and a lack of ovarian oestrogen production therefore appears to explain the lack of an LH response to ovariectomy during lactation.

Ovarian positive feedback

Ovulation can be achieved only if the course of follicular growth and maturation has been completed up to the preovulatory stage and if the hypothalamo-pituitary axis can respond to the high levels of oestrogens by a discharge of LH.

In early lactation (first week pp), treatment with oestradiol benzoate (OB) is ineffective in stimulating LH secretion (Elsaesser and Parvizi, 1980; Cox *et al*, 1988). Between the third and fourth week of lactation, there is a partial recovery of the positive feedback response to OB (Cox *et al*, 1988; Elsaesser *et al*, 1992; Sesti and Britt, 1993). However, even with a massive dose of OB (60 μ g/kg body weight), the amplitude of the LH peak remains much lower than that observed in cyclic or OB-treated prepubertal females (Elsaesser and Parvizi, 1980). Failure to activate positive feedback in early lactation could be due to a low pituitary pool of releasable LH. Lack of responsiveness of the sow to a low dose of OB (6 μ g/kg body weight) in the first weeks after parturition may also be due to a high metabolic clearance rate of oestrogens preventing oestradiol-17 β from reaching the threshold level (Cox *et al*, 1988). Finally, in lactating sows, the hormones and neurotransmitters associated with suckling could block the discharge of GnRH and that of LH in response to high levels of oestrogens. In weaned sows, the duration of lactation influences the responsiveness to OB; the amplitude of the oestrogen-induced LH surge is higher after 35 than after 21 or 10 d of lactation (Edwards and Foxcroft, 1983b; Kirkwood *et al*, 1984b).

Pituitary responsiveness to GnRH

The pituitary gland of lactating sows remains responsive to GnRH, because intravenous injections of GnRH stimulate the release of LH and FSH (Bever *et al*, 1981; Stevenson *et al*, 1981; Cox and Britt, 1982b; Rojanasthien *et al*, 1987b; De Renzis *et al*, 1991). From the first to second and third weeks of lactation, the secretion of LH after GnRH treatment increases, indicating a change in the pituitary responsiveness (Bever *et al*, 1981; Rojanasthien *et al*, 1987b).

Influence of lactogenic hormones on gonadotrophin secretions

In lactating sows, Tokach *et al* (1992a) have shown that the mean concentration of plasma insulin as early as day 7 pp was positively correlated with the number of LH peaks observed at days 14 and 21 pp. In feed-restricted prepubertal gilts, increasing insulin concentrations by glucose infusion restores LH pulsatility to the level observed in well-fed females (I'Anson *et al*, 1991). Therefore, low insulin concentrations may contribute to the inhibition of LH in lactating sows. This hypothesis was tested by infusing glucose to lactating sows on day 18 pp for 12 h (Tokach *et al*, 1992b). Insulin concentrations increased (x 3) whereas mean LH concentration and pulsatility did not change. However, females received a meal every 24 h and insulin before treatment never fell as low as in feed-restricted animals.

An inverse relationship has generally been reported between LH and prolactin. This may be explained by the fact that the opioids released at suckling inhibit both GnRH and dopamine secretions and that dopamine itself inhibits prolactin release (Kraeling *et al*, 1982). Alternatively, prolactin may act directly at the hypothalamic level. This is supported by the results from

Booman *et al* (1982), who found that mean and basal LH concentrations and the frequency of LH pulses just after weaning are lower in sows treated with prolactin than in control sows. Pituitary sensitivity to GnRH does not seem to be influenced by prolactin, because Bever *et al* (1981) have demonstrated that the LH-response to an injection of GnRH is not correlated with prolactin levels at the time of treatment.

In prepubertal gilts, daily injection of GH (90 µg/kg body weight) reduces the oestradiol-induced release of LH (Kirkwood *et al*, 1988). Data are lacking in lactating sows.

Ovarian responsiveness to gonadotrophins

It is unknown whether lactation induces modifications in follicular LH and FSH receptors and in their binding activity. Two days after weaning, theca and granulosa binding of hCG increases with stage of follicular development (Foxcroft *et al*, 1987). During lactation, the ovaries are responsive to gonadotrophins since it is possible to induce ovulation by exogenous gonadotrophins or GnRH during lactation (see review by Britt *et al*, 1985; Rojanasthien *et al*, 1988). However, the percentage of treated sows exhibiting oestrus and conceiving increases after the third week of lactation. This higher responsiveness may be related to the larger size and number of follicles, which was previously described.

Influence of lactogenic hormones on ovarian activity

In vitro studies have essentially demonstrated that both insulin and IGF-I are important modulators of follicular maturation (see reviews by Adashi *et al*, 1985; Hammond *et al*, 1993). These studies have shown that insulin regulates growth and maturation of granulosa cells, operates in synergy with

FSH to induce LH receptor synthesis and stimulates the production of progesterone by pig granulosa cells (Channing *et al*, 1976). IGF-I has been shown to stimulate proliferation and differentiation of granulosa cells and to operate in synergy with FSH in the induction of granulosa cells aromatase activity (Adashi *et al*, 1985). Thus, insulin and IGF-I may have a key role in mediating nutrition–reproduction interactions. In underfed prepubertal gilts, refeeding increases follicular fluid IGF-I concentrations (Charlton *et al*, 1993). In cyclic gilts, insulin treatment increases ovulation rate even without a concomitant rise in LH secretion (Cox *et al*, 1987b). In fact, insulin reduces atresia and increases intrafollicular IGF-I of medium follicles (4–6 mm) (Mata-moros *et al*, 1991). Therefore, in lactating sows with a nutritional deficit, circulating concentrations of insulin and IGF-I may be insufficient for a normal folliculogenesis.

The high GH concentrations occurring in some lactating sows could also play a role. In mature gilts, both stimulatory and inhibitory effects of exogenous GH on ovulation have been demonstrated (Kirkwood *et al*, 1988). In cultured porcine granulosa cells, GH enhances the stimulatory effects of oestradiol-17 β and FSH on progesterone secretion (Hsu and Hammond, 1987). This action may be mediated by the increase in IGF-I production by these cells (Hsu and Hammond, 1987).

Conclusion

There are large differences between the patterns of LH and FSH secretion during the course of lactation and around weaning. In the pituitary gland, LH but not FSH synthesis is depressed during lactation. Circulating concentrations of LH increase from the 3rd week of lactation and again after weaning (fig 6), whereas variations in FSH are less marked. This divergence is probably related

to different types of control. Secretion of FSH is mostly controlled by ovarian negative feedback. LH is mainly regulated by suckling-induced neuroendocrine reflexes, which inhibit GnRH release and by endocrine mechanisms influenced by the metabolic balance (fig 6). These 2 different mechanisms result in a complex regulation of LH secretion. Therefore, the intensity of udder stimulation and of the nutrient deficit will both influence LH secretion during lactation. However, at the beginning of lactation (3–14 d pp), when udder stimulation is maximal, we can hypothesize that the LH inhibition related to the suckling-induced neuroendocrine reflexes is dominant. During the 3rd and 4th weeks pp, when milk production is maximal and suckling stimuli are lower, the relative influence of the nutrient deficiency on LH secretion increases. However, the increase in LH secretion during the 3rd week of lactation suggests that the inhibition due to the nutritional deficit is not as powerful as that due to suckling. FSH secretion and its control during lactation remain debatable and the importance of the inhibin role needs to be established.

As lactation progresses, folliculogenesis is more and more active, but follicles do not reach the preovulatory stage. This partial blockade is due, at least in part, to insufficient gonadotrophin support. Influence of other hormones acting directly at the ovarian level and depending on suckling-related stimulation and/or on the nutritional balance may also be involved.

DELAYED OESTRUS AFTER WEANING

Some sows, particularly primiparous sows, fail to return to oestrus within 10 d after weaning. Causes of this disturbance of reproductive activity are multiple and may result from endogenous, nutritional and environmental factors. Among the endogenous factors, parity, genotype and duration of lac-

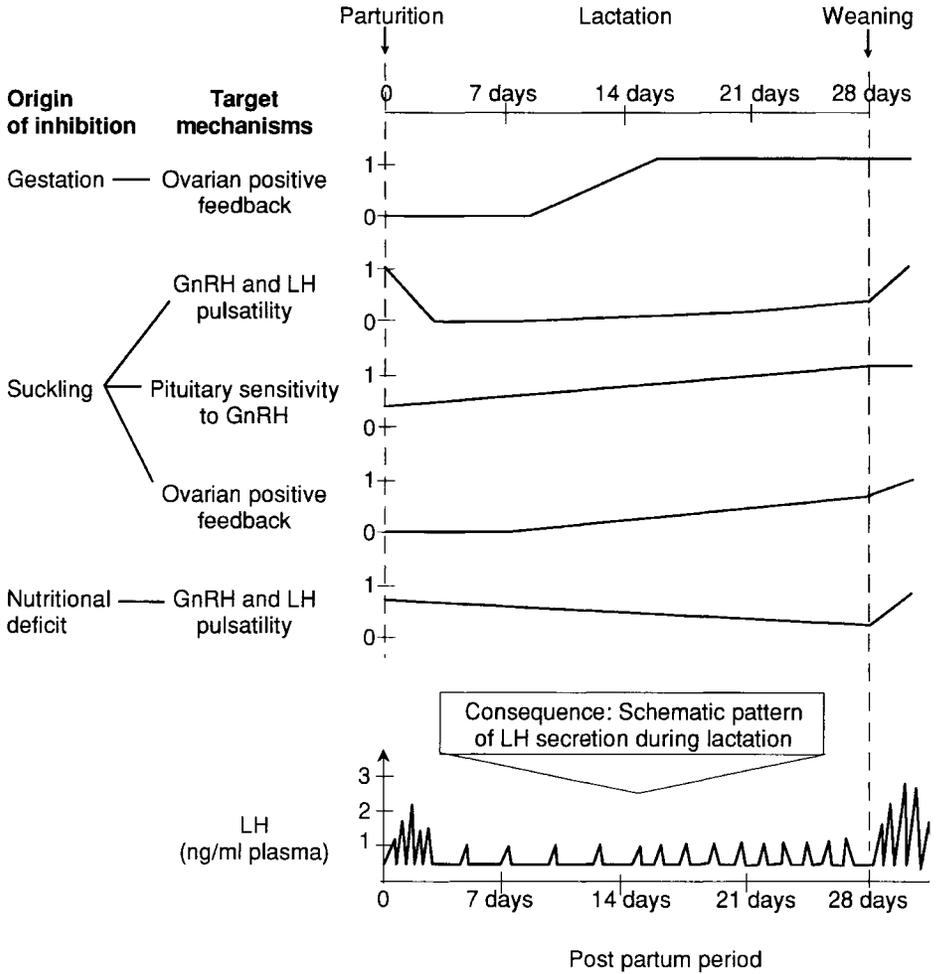


Fig 6. Schematic representation of LH inhibition in the pp period: origins and schematic pattern. Arbitrary scale from 0 (inhibited mechanism) to 1 (fully functional mechanism).

tation play an important role (Aumaître *et al*, 1976; Varley and Cole, 1976; Maurer *et al*, 1985). Nutritional influence is particularly important and it seems that there is a critical energy intake during lactation, below which return to oestrus after weaning is delayed, in relation to the loss of body fat during lactation and/or the absolute amount of fat reserves at weaning (see reviews by King, 1987; Dourmad *et al*, 1994). Among the

environmental factors, season and, particularly, light duration and ambient temperature are powerful modulators (Armstrong *et al*, 1986b; Prunier *et al*, 1994).

Endocrine mechanisms implied in altered return to oestrus after weaning are not clear. It has been established that delayed oestrus is not due to an hyperprolactinaemic state after weaning (Van de Wiel *et al*, 1978; Shaw and Foxcroft, 1985; Armstrong *et al*,

1986a). Gonadotrophin or oestrogen treatment, or pulsatile GnRH administration, can induce oestrus and ovulation, but a variable proportion of anoestrus sows fail to respond properly (Dial *et al.*, 1984; Armstrong and Britt, 1985). Therefore, the hypothesis of a complete blockade at the ovarian and/or pituitary levels must be excluded.

Delayed return to oestrus may result from dysfunction at the hypothalamo-pituitary level and/or directly at the ovarian level. In sows with delayed oestrus after weaning, LH secretion is lower during lactation than in sows with normal return to oestrus, whatever the reason associated with the delayed oestrus (non-specific: Shaw and Foxcroft, 1985; undernutrition: King and Martin, 1989; Armstrong *et al.*, 1986a; Tokach *et al.*, 1992a; temperature: Barb *et al.*, 1991). In females with normal or delayed return to oestrus, LH secretion rises immediately after weaning whatever the reason associated with the delay (non-specific: Shaw and Foxcroft, 1985; season: Armstrong *et al.*, 1986b; undernutrition: King and Martin, 1989; Tokach *et al.*, 1992a). However, mean concentration of LH and pulsatility are lower on the day following weaning in sows with a longer weaning-to-oestrus interval, even though the difference is not always significant. The low LH secretion occurs simultaneously with a decrease in hypothalamic GnRH content suggesting altered activity at the hypothalamic level (Armstrong *et al.*, 1986b). In sows remaining in anoestrus after weaning, ovariectomy is followed by an increase in LH mean level and pulsatility (Almond and Dial, 1990a). Moreover, treatment with oestrogens results in lower LH mean concentrations and pulsatility in ovariectomized sows remaining in anoestrus than in those returning to oestrus after weaning (Almond and Dial, 1990b). Therefore, these authors have suggested that increased sensitivity of the hypothalamo-pituitary axis to the negative feedback of oestrogens is implicated in the post-weaning anoestrus.

Follicular populations of sows with delayed oestrus after weaning have been poorly characterized before and after weaning. An abnormal response of the follicles to LH stimulation after weaning is suggested by the observation of relatively low peripheral concentrations of testosterone and oestradiol-17 β within 24 h after weaning in sows with delayed oestrus which may or may not be related to undernutrition (undernutrition: Kirkwood *et al.*, 1987; non-specific: Prunier *et al.*, 1993). Moreover, in sows weaned in the summer, a longer weaning-to-oestrus interval is associated with aberrant post-weaning patterns of plasma oestradiol-17 β in a high proportion of females (Armstrong *et al.*, 1986b).

Metabolic hormones, whose influence on the gonadotrophic axis has been previously discussed, may be involved in delayed oestrus. Preprandial concentrations of glucose and free fatty acids are respectively higher and lower 12–20 d after weaning in sows with longer weaning-to-oestrus intervals (Armstrong *et al.*, 1986a). Thus, alteration in energy metabolism after weaning may predispose sows to the occurrence of anoestrus. Mean plasma insulin during lactation (days 7 and 21 pp) is lower in sows with delayed return to oestrus (Tokach *et al.*, 1992a). This suggests a role for insulin in anoestrus. However, in primiparous sows, injections of insulin around weaning were inefficient at stimulating post-weaning oestrus (Rojkittikhun *et al.*, 1993), but, in these experiments, lactational body weight loss was very low in treated sows and the weaning-to-oestrus interval was short in control females.

High ambient temperatures seem to alter return to oestrus after weaning (Prunier *et al.*, 1994). When lactating sows are kept at 30°C rather than 22°C, the secretion of GH is increased whereas that of cortisol is decreased, suggesting a role for these hormones in delayed oestrus after weaning (Barb *et al.*, 1991; Prunier *et al.*, 1994).

In summary, multiple physiological factors are likely to play a role in the failure of sows to rapidly return to oestrus after weaning. Insufficient gonadotrophin support to folliculogenesis during lactation and/or after weaning, as well as lack of responsiveness of the ovaries to LH stimulation immediately after weaning, might be involved. In both cases, alterations in metabolism may have predisposed the sows to the occurrence of postweaning anoestrus.

CONCLUSION

A period of anovulation occurs after farrowing in the sow. Gestation and farrowing are involved in suppressing the return to ovulation until the beginning of the third week pp. During lactation, suckling-induced neuroendocrine reflexes are the main factors inhibiting LH secretion and pp ovulation (fig 6). Negative metabolic state due to high milk production creates a hormonal background, which may constitute an additional inhibitory factor (fig 7). The effects of udder stimulation seem to be dominant 3–14 d pp with effects of the metabolic consequences of lactation being more evident during the third and fourth weeks pp. During the course of lactation, LH secretion increases and folliculogenesis is more and more active. As a consequence, the hypothalamo–pituitary–ovarian axis becomes able to respond properly to the stimuli associated with weaning, which normally allows the sow to start a follicular phase and ovulate within a week.

The reasons for delayed oestrus after weaning have not been fully elucidated. Insufficient secretion of LH during lactation or immediately after weaning, as well as lack of responsiveness of the ovaries to the endocrine changes associated with weaning, have been proposed to play a role. However, the relative importance of these mechanisms and their degree of interdependence are not known. Hormones such

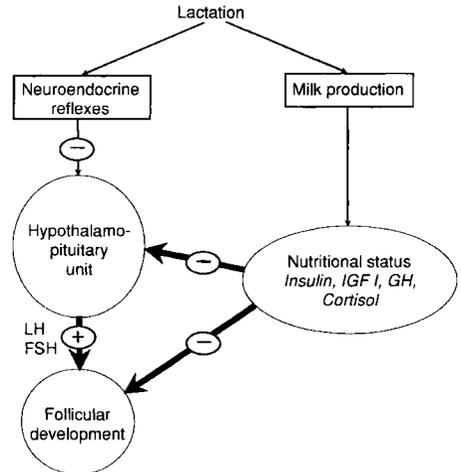


Fig 7. Consequences of lactation on the gonadotrophic axis.

as prolactin, insulin, GH and IGF-I vary with nutritional and environmental factors influencing the weaning-to-oestrus interval and are probably involved (fig 7). These hormones may act at the hypothalamo–pituitary level and/or directly at the ovarian level. Thus, their influence should be evaluated at both levels in future studies.

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