Endocrine Control of Lactational Infertility. I

*Alan S. McNeilly, *Anna Glasier, and †Peter W. Howie

*MRC Reproductive Biology Unit, Edinburgh EH3 9EW, and †Department of Obstetrics and Gynaecology, University of Dundee Medical School, Ninewells Hospital, Dundee DD1 951, Scotland

Although there is no doubt that breastfeeding suppresses ovarian activity, the reasons for the immense variability in the duration of this suppression and the mechanisms by which the suckling stimulus causes it remain unclear. The interbirth interval in women who breastfeed can be divided into three main components: (a) the period of lactational amenorrhoea, (b) a period when menstruation returns either during or after lactation, and (c) pregnancy. The length of periods a and b will vary considerably depending on the pattern of breastfeeding, and in a few cases pregnancy will occur during the period of lactational amenorrhoea without an intervening period of menstrual cycles. In an attempt to clarify the mechanisms controlling each of periods a and b above, the changes in endocrine and ovarian activities will be explored.

GONADOTROPHIC CONTROL OF THE MENSTRUAL CYCLE

Before discussing in detail the influences of suckling on ovarian activity, it is first necessary to outline the basic mechanisms controlling the growth and development of follicles and subsequent formation of the corpus luteum in the normal menstrual cycle. The basic changes in the four principal hormones involved are shown in Fig. 1.

At the time of menses following the demise of the corpus luteum of the previous cycle, follicle development starts, and usually a single follicle begins to grow. This growth is initiated by the pituitary gonadotrophin follicle-stimulating hormone (FSH). The continuation of growth, although requiring the continued presence of FSH, is dependent on oestradiol secreted from the growing follicle in response to luteinizing hormone (LH). LH is released in a pulsatile manner from the pituitary, the frequency of these pulses increasing through the follicular phase of the cycle. This increase in LH-stimulated oestradiol secretion, together with the continued stimulation of FSH, stimulates follicle growth and increased oestrogen secretion. Around midcycle, when the single dominant follicle is approximately 18 to 22 mm in diameter, the increase in oestradiol secretion is sufficient to trigger the release
Fig. 1. Schematic diagram of the endocrine changes during the menstrual cycle. Note that the initial growth of the follicle is due to an increase in FSH around menstruation, whereas continued follicle growth occurs in response to oestradiol. This is secreted by the follicle in response to pulses of LH, the frequency of which increase towards midcycle. The increase in oestradiol triggers the preovulatory surge of LH, which induces ovulation, and transformation of the follicle into the corpus luteum, which secretes progesterone.

Of the preovulatory surge of LH and FSH. This temporarily inhibits ovarian steroid secretion, alters the steroidogenic machinery of the follicle to make it secrete predominantly progesterone (luteinization); and some 36 hr after the start of the LH surge, ovulation occurs, with the oocyte being ejected from the follicle. The follicle then collapses and forms the corpus luteum, which, under the influence of LH, secretes progesterone and oestradiol (Fig. 2).

Of critical importance to this sequence of events is the maintenance of LH secretion in the follicular phase of the cycle. As mentioned above, LH is released in a pulsatile manner from the pituitary. This occurs as a result of pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, reaching the pituitary gland via the hypophysial portal blood system.

While the overall controller of GnRH release remains to be determined, it is sufficient to think in terms of a hypothalamic GnRH pulse generator, the frequency of which is modulated by the ovarian steroids. Thus, oestradiol appears to increase the GnRH pulse secretion, whereas progesterone and oestradiol decrease pulse release.

In many amenorrhoeic states pulsatile secretion of LH, which can be measured, is abnormal, either slow or absent. Many of these states can be treated by pulsatile infusion of GnRH delivered subcutaneously or intravenously by a minipump worn by the patient.
FIG. 2. Schematic diagram of the hypothalamic control of gonadotrophin secretion. Note that GnRH is released in pulses from the hypothalamic pulse generator and induces pulsatile LH release from the pituitary. The subsequent sequence of events in terms of follicle development is outlined in Fig. 1. It is envisaged that suckling either via a direct neural input and/or by increasing prolactin secretion alters the frequency of LH pulse secretion by affecting the hypothalamic GnRH pulse generator.

In lactation a similar alteration in the pulsatile secretion of GnRH has also been identified, suggesting that the principal site where suckling affects ovarian activity is at the hypothalamic GnRH pulse generator.

LACTATIONAL AMENORRHOEA

Recovery from Pregnancy

During pregnancy, the high circulating plasma levels of placental steroids suppress pituitary levels of both LH and FSH to approximately 1% of normal (1), whereas the increase in oestrogen secretion substantially increases the number of lactotrophes in the pituitary and plasma levels of prolactin (2). Following parturition and the clearance of these steroids, pituitary and plasma prolactin levels decline, and plasma levels of FSH and LH increase within 30 days in a non-breastfeeding woman (3–5). This resumption of the pulsatile secretion of LH (6) leads to an early return of follicle growth and menstruation, although first menstruation is usually preceded by an inadequate (80%) or absent (20%) luteal phase in terms of pregnanediol secretion (7). Luteal function subsequently improves, so that by the third
postpartum cycle, normally between 70 and 120 days postpartum (8), the majority of cycles (88%) have normal luteal function (7).

Thus, the delay in the resumption of normal ovulatory cycles in non-breastfeeding women depends mainly, if not exclusively, on the time taken for the recovery of the hypothalamo-pituitary-ovarian axis from the suppressive effects of pregnancy.

Suppression of Ovarian Activity

The results in non-breastfeeding women suggest that even limited corpus luteum function will result in the recurrence of menstruation. Thus, it can be assumed that during lactational amenorrhoea ovarian activity is sufficiently suppressed that ovulation normally does not occur. Assessment of follicular development either in terms of plasma levels of oestradiol (3-5) or total urinary oestrogen (8-10) confirm that follicular development rarely occurs during lactational amenorrhoea (Fig. 3). More recently we have confirmed by ultrasound the absence of medium- or large-sized follicles within the ovary in breastfeeding women (11). However, although urinary oestrogen levels are below those which would indicate follicular development equivalent to that seen around day 5 to 7 of the normal menstrual cycle, we have recently observed, by estimation of urinary oestrogens in daily early morning urine specimens, that there may be periods during which follicle growth is initiated, indicated by a rise in oestrogen, but not sustained.

![Graph showing changes in urinary total oestrogens and pregnanediol in relation to the suckling frequency and duration and plasma levels of prolactin in a breastfeeding woman. Note that even at four feeds each day with a suckling duration of 50 min/day, follicular development in terms of oestrogen is below the lower limit of normal (10 μg/24 hr), whereas prolactin remains at or above the upper limit of normal (500 mU/liter). First menstruation is not preceded by ovulation, and the four subsequent cycles have inadequate corpus luteum function. (From ref. 12.)](image-url)
It is clear that the period of lactational amenorrhoea is dependent on the suckling input (2,12). While this is maintained, ovarian activity is suppressed. However, the amount of suckling input is very difficult to define, since suckling patterns vary considerably among different societies. In our own study group of over 70 women in Edinburgh, a suckling frequency of more than five times and more than 65 min (minimum, 10 min per feed) each day is sufficient to maintain complete suppression of ovarian activity (7,13). Any decrease below these limits in either suckling frequency or duration results in the resumption of follicular development. A longitudinal study in Denmark also suggests that suckling five times each day is the minimum required to protect against pregnancy in developed countries (14). While further studies of women in Edinburgh have confirmed our findings, similar longitudinal studies in other societies must be undertaken to determine the parameters necessary for maintenance of lactational amenorrhoea. It is probable, with a frequency which is considerably greater than the Edinburgh norm, that duration of each individual suckling episode may lose importance in maintaining amenorrhoea.

It is well known that suckling causes the release of prolactin, that the amount of prolactin released appears to decline with time postpartum (1,2), and that there is a close correlation between basal plasma levels of prolactin and both suckling frequency (2-4) and duration (8,9). Although during the period of lactational amenorrhoea both suckling frequency and duration are maintained (9,10), there is a gradual decline in basal levels of prolactin. However, basal levels remain above the upper limit of those in the menstrual cycle (Fig. 3). More recently we have shown that the amount of prolactin released during suckling in the afternoon is significantly greater than in the morning (15) (Fig. 4). Since both the feed volume and duration of suckling were the same, this suggests that there may be a difference in sensitivity of the hypothalamic releasing mechanism for prolactin in response to suckling. A diurnal variation in prolactin secretion is well recognized in non-lactating women (16). This may be of considerable significance, since amenorrhoea appears to be prolonged if night feeds are maintained (12).

In spite of the close correlation between suckling-induced hyperprolactinaemia and lactational amenorrhoea (8,17,18) the mechanism by which suppression of ovarian activity occurs remains uncertain. Normal follicular development depends on both FSH and LH. Previous studies during lactational amenorrhoea have demonstrated that injection of GnRH results in a normal increase in both LH and FSH by 30 to 40 days postpartum (see ref. 1), indicating that there is sufficient gonadotrophin reserve in the pituitary for normal gonadotrophin secretion. Indeed, in breastfeeding, as in non-breastfeeding women, plasma levels of FSH recover rapidly and are within the normal menstrual cycle range within 20 to 30 days postpartum (3-6). Thus, it is improbable that a lack of FSH can be responsible for the failure of ovarian development.

On the other hand, basal levels of LH do appear to be reduced in the majority of women during lactational amenorrhoea (2,6,19). However, in the normal menstrual cycle, LH is released in a pulsatile manner (20-22) as a result of a pulsatile release of GnRH from the hypothalamus, and the frequency of pulses appears to
Changes in suckling frequency and basal plasma levels of prolactin with time postpartum and the prolactin response to suckling during this period. The time of introduction of supplements (S), onset of follicular development (F) and of ovulation (O) are indicated. At 10 (A), 17 (B), 27 (C), and 40 (D) weeks, blood samples were collected at 15-min intervals for 6½ hr. The onset of suckling is indicated (V). Note that when suckling occurred, the prolactin response was greater in the afternoon than in the morning. (From ref. 15.)

be of critical importance for follicle development (23,24). Previous reports have suggested that there is a reduction in or absence of pulsatile LH secretion in women with lactational amenorrhoea (25–28). We have recently confirmed that there is a suppression of the basal levels of LH, which is related to low-frequency, low-amplitude pulses of LH (19). However, this was found in only 70% of the observation periods during lactational amenorrhoea. In the remaining 30% of periods, basal levels and pulse amplitude and frequency of LH were similar to those in the follicular phase of the subsequent normal menstrual cycles in these women (19). This pulsatile secretion was also associated with an increase in urinary levels of oestrogen, indicating follicle development, although the levels of oestrogen did not rise into the range seen in the early follicular phase of the cycle (A. Glasier and A. S. McNeilly, unpublished observations), indicating that follicular development was not sustained as in the normal cycle (29). It has been shown previously that breastfeeding women are more sensitive to the negative feedback effects of
oestrogen than are non-lactating women (30,31) and fail to show the normal positive feedback response (Fig. 5).

It should also be remembered that if the hypothalamic GnRH neurons were not under any inhibition, then LH levels in breastfeeding women who have very low levels of oestrogen should be in the postmenopausal range. Clearly, this is not the case, suggesting that there is a reduced ability of the hypothalamus to release GnRH. Thus, although apparently normal pulsatile LH secretion occurs 30% of the time during lactational amenorrhoea and can stimulate ovarian oestrogen secretion, it is probable that this low level of oestrogen is sufficient to switch off the reduced GnRH release at the hypothalamus, preventing further LH release and terminating follicular development (19,29; Fig. 6).

The question that arises is whether the neural suckling stimulus alone is responsible for the suppression of GnRH release or whether it operates in combination with the raised levels of prolactin. Since prolactin and suckling are so closely related, this question remains unresolved.

In amenorrhoeic patients presenting with a prolactin-secreting pituitary tumour, resumption of menstruation and pregnancy can be induced by normalization of prolactin, either by surgical removal of the tumour or treatment with pharmacological dopamine receptor agonists such as bromocriptine (1,2). This suggests that high levels of prolactin, as seen in lactation, could be responsible for the suppression

---

FIG. 5. The concentration of FSH and LH in plasma of seven breastfeeding (○--○) and seven non-breastfeeding (●--●) women before and after the injection of 1 mg oestradiol benzoate (E2B) at 100 days postpartum. Results are expressed as a percentage of the mean basal values before injection. In non-lactating, non-breastfeeding women, all of whom had resumed normal menstrual cycles, E2B induced negative and positive release of LH and FSH. In contrast, breastfeeding women failed to show a positive feedback response but had a significantly enhanced negative feedback response. (From refs. 30 and 50.)
**FIG. 6.** Diagrammatic representation of the control of gonadotrophin secretion and interaction with prolactin during lactational amenorrhoea and resumption of follicular growth and ovulation in breastfeeding women. Suckling causes a decrease in hypothalamic capacity to release GnRH, with subsequent reduced pulsatile secretion of LH (1) in the face of high prolactin levels. Pulsatile secretion of LH occurs 30% of the time in lactational amenorrhoea and initiates follicular development with an increase in oestrogen secretion (2). However, because of the increase in sensitivity to the negative feedback effects of this oestrogen, probably because of the reduced hypothalamic capacity to release GnRH, pulsatile LH secretion is switched off (2) and further LH secretion is inhibited (3). This process continues until the suckling stimulus and prolactin levels decrease (5,6), at which time hypothalamic capacity returns to normal with normal negative/positive feedback action of oestrogen, allowing maintained pulsatile LH secretion and sustained follicular growth, ovulation, and luteal function (7). (From ref. 50.)

of GnRH and LH secretion, since the pattern of LH secretion is often similar to that in hyperprolactinaemic patients (25,32). However, the aetiology of pituitary tumours remains unknown (33), so the relevance of these observations remains questionable.

Similarly, it has been suggested that prolactin might act directly on the hypothalamus to increase turnover of dopamine, the prolactin-inhibiting factor (34). Such a short-loop feedback system, by which prolactin controls its own secretion, appears to operate in primates as well as in rodents (34). Since an increase in dopamine will also suppress the secretion of LH in women, it is possible that the raised levels of prolactin induced by suckling might suppress GnRH and LH secretion by an increase in dopamine. However, recent studies in the rat (35,36) have shown that lactation is associated with a significant reduction in basal hypothalamic dopamine turnover, casting considerable doubt on the theory of dopamine-mediated suppression of GnRH secretion.

Thus, it may be that the raised levels of prolactin merely reflect the strength of the suckling stimulus, although how this is relayed through the hypothalamic-
pituitary axis is not yet clear. Clearly, maintenance of the suckling stimulus is all important. In our own studies, suckling frequency and duration are both important, although duration may become so only when frequency is low. This remains to be determined. Similarly, the pattern of suckling during each suckling episode may also be important in determining how effective suckling will be in releasing prolactin and suppressing gonadotrophin release. This has yet to be investigated and may prove to be of considerable importance, since it has recently been shown that the suckling rate will vary depending on milk flow (37). Changes in milk flow and suckling patterns in women with lower than normal milk outputs have yet to be studied and may be of considerable importance in determining the effectiveness of suckling in suppressing ovarian activity.

Resumption of Ovarian Activity

At some stage during lactational amenorrhoea, follicle growth occurs and is sustained. Cross-sectional studies have not been able to define any specific change which can explain the transition from a failure to a maintenance of follicular growth. However, in our own longitudinal studies it is now clear that resumption of follicular development is associated with a decrease in the frequency and/or the duration of the suckling stimulus (8,10). This is most dramatically caused in some women by the introduction to the baby of supplementary food (8) which, in about half of the women we have studied, resulted in a significant decrease in suckling duration without an immediate change in suckling frequency (8; Fig. 7). This decrease in suckling input resulted in a significant decrease in plasma levels of prolactin (8,38) but no change in plasma levels of LH or FSH (6,9,19). The resumption of ovarian activity was also independent of time postpartum (and therefore of infants’ age), occurring over a range between 14 and 82 weeks postpartum, and of maternal body weight (8,9,39).

Whether the introduction of supplementary food to the baby resulted in resumption of follicular development depended on the impact on suckling behaviour (8). If suckling declined rapidly, then not only did follicular development occur but ovulation also resumed (Fig. 7). In contrast, if supplements caused only a small reduction in suckling, then prolactin levels fell more slowly, and follicular development and ovulation were delayed for a further variable time (8,10; Fig. 7).

Ovulation and Pregnancy During Amenorrhoea

There is some dispute about the frequency of ovulation in the cycle before the end of lactational amenorrhoea, the estimates varying from 14% (40), 23% (41), and 33% (8) to 75% (42). These different estimates may be partly explained by the different methods used to assess ovulation (12) but are more likely due to the different suckling patterns of the populations studied. It has been shown that the longer the first menses is delayed during lactation, the more likely is the first cycle to be ovulatory (8,42). In addition, our own studies suggest that continuation of night feeds will also delay the onset of ovulation (Fig. 8).
FIG. 7. Comparison of infant feeding patterns and basal prolactin between (○) mothers ovulating within 16 weeks (n = 14) and (●) mothers suppressing ovulation (n = 13) after introduction of supplementary food. Values are mean ± SEM. The broken line indicates the upper limit of prolactin for non-pregnant women. *P<0.01 from marked time point onwards. (From ref. 8.)

Resumption of ovulation after prolonged lactational amenorrhoea may result in conception rates of up to 10% (43). To our knowledge, the changes in hormonal status and suckling parameters have been documented in only three cases (4,13). In all of these, ovulation and pregnancy occurred after follicular development resumed when suckling was dramatically reduced (4,13). Thus, much more effort should be directed to documenting the changes in suckling patterns around the time of any conception occurring during lactational amenorrhoea, since there is no
recurrence of menstruation to warn of the impending return of fertility. This can be done only by longitudinal tracking of breastfeeding women who do not use contraception. Cross-sectional studies will not provide an answer.

**MENSTRUATION DURING LACTATION**

It is now clearly established that corpus luteum function in first complete menstrual cycles in breastfeeding women is associated with inadequate progesterone secretion (7,9,17,18,44; Figs. 3 and 9). Indeed, in a total of 49 menstrual cycles occurring during lactation we found that pregnanediol levels in the luteal phase were within normal limits in only 13 (27%) cycles, the remainder of the luteal phases being deficient (31%) or absent (42%). The proportion of normal luteal phases remained low during the first cycles after lactation (6/23) but rose to 24/31 in subsequent cycles (7). Thus, the continuation of the suckling stimulus and the associated marginal hyperprolactinaemia appear to influence luteal function after ovulation. A similar inadequacy of luteal function in first cycles postpartum in non-breastfeeding mothers has also been reported (7,45) and did not appear to be related to excessive plasma levels of prolactin.

Nevertheless, our own studies suggest that maintenance of suckling, once ovulatory menstrual cycles have resumed, leads to a prolonged series of inadequate luteal phases (7,13; Fig. 3). In several instances, the maintenance of night feeds with only token suckling during the day appeared sufficient to reduce luteal function (13).
In non-breastfeeding women it has been suggested that inadequate corpus luteum function results from a reduction in the FSH-LH ratio around the time of menses, i.e., 10 to 15 days before ovulation (46). Plasma levels of FSH are always at the upper limit of normal (3–6). However, basal plasma levels of LH appeared to be marginally lower than normal during inadequate luteal phases (6), although the pulsatile secretion of LH appeared to be normal (19).

More recently we have measured the changes in urinary steroids and gonadotrophins in early morning urine specimens collected daily during lactational amenorrhoea, through a series of inadequate luteal phases during breastfeeding, until the return of normal menstrual cycles (A. Glasier and A.S. McNeilly, unpublished observations). In all 8 cases involving 19 inadequate luteal phases, the increase in oestrogens in the follicular phase was similar regardless of subsequent luteal function (Fig. 10), suggesting that follicular development was normal. In contrast, there was a progressive increase in the amount of pregnanediol excreted during the luteal phase in consecutive menstrual cycles, showing a gradual improvement in corpus luteum function with successive cycles. This was associated with a progressive decline in suckling, until complete weaning occurred and normal luteal function was achieved. This progressive improvement was also associated with a progressive increase in the amount of LH released during the midcycle preovulatory surge (Fig. 10).

Thus, it would appear that suckling can in some way disrupt the normal generation of the preovulatory surge and result in a failure to discharge normal amounts of LH around the time of the final maturation of the preovulatory follicle and may be the cause of the subsequent inadequate corpus luteum function. If this were the case, then it could be envisaged that the duration of menstrual cycles with inadequate corpus luteum function is dependent on the duration of concomitant suckling activity, perhaps in particular night-time feeds. We have previously shown that prolactin response to suckling is greater in the afternoon than the morning (15).
FIG. 10. Changes in urinary oestrogen (E:C), pregnanediol (P:C), and LH (LH:C) in early morning urine specimens collected daily throughout consecutive menstrual cycles over the transition from lactational amenorrhoea to menstruation. Results are corrected and reported in terms of units per gram of creatinine. Menstruation is indicated by the solid bar. Note that whereas there is little difference in oestrogen secretion before each rise in pregnanediol, total pregnanediol excretion in the second cycle is greater than in the first cycle. Similarly, there is a significant increase in the amount of LH released around midcycle. (A. Glasier and A. S. McNeilly, unpublished observations.)

More recently it has been established that in the normal menstrual cycle the start of the preovulatory surge of LH occurs at night in the majority of women (47,48). Thus, it is tempting to speculate that night-time suckling is more likely to suppress the generation of a normal preovulatory LH surge, thus leading to the formation of an inadequate corpus luteum. While the suckling stimulus is maintained, inadequate luteal function will occur. Clearly, this will require considerable further investigation, since the causes of inadequate corpus luteum function in the menstrual cycle are almost certainly a complex of endocrine changes. It also remains possible that the high levels of prolactin might directly inhibit follicular development at the ovarian follicle, but there is no clear evidence to support this in women (49,50).

CONCLUSIONS

Our studies conclusively confirm that breastfeeding, even in an industrialized, well-nourished population, will suppress fertility for a considerable period of time (up to 75 weeks). Resumption of ovarian follicular development and ovulation occurs only when suckling frequency decreases below five feeds each day, with a total daily suckling duration of less than 65 min/day. Ovulation will resume if total suckling activity is below this level, even if no supplementary food is being given and the baby is receiving breast milk as its sole source of nutrition.

The resumption of follicular development and ovulation occurs when there is a significant decrease in suckling input below that indicated above. This can be
precipitated by introduction of supplementary food, presumably by reducing the baby's dependence on breast milk; but resumption of ovarian activity is not dependent on age of baby or maternal body weight.

First menstrual cycles are normally associated with inadequate luteal function, which tends to continue if suckling is maintained. Rapid reduction in suckling, or weaning, especially if occurring after prolonged lactation, can result in ovulation with normal luteal function, with the potential to carry a pregnancy if conception occurs. This appears to explain the occurrence of pregnancies during lactational amenorrhoea in the cases where adequate data is available.

Reduction in the pulsatile secretion of LH appears to be mainly responsible for the absence of follicular development during lactational amenorrhoea. Whereas pulsatile LH secretion may occur between 20 and 30% of the time and stimulate limited follicular development, suckling appears to reduce the ability of the hypothalamus to maintain pulsatile GnRH and hence LH secretion, and follicular development ceases.

Inadequate corpus luteum function appears to be related to plasma levels of prolactin above normal and to a reduced midcycle surge of LH. Suckling may directly interfere with the generation of a normal preovulatory LH surge, whereas prolactin may interfere directly at the ovarian level to suppress ovarian response to gonadotrophins. However, the mechanisms whereby the suckling stimulus decreases GnRH output from the hypothalamus remain unknown. It is clear that the maintenance of infertility during breastfeeding is directly dependent on the strength of the suckling stimulus. Anything that undermines or reduces this stimulus will result in a resumption of ovarian activity with a variable return in fertility.

ACKNOWLEDGEMENTS

We wish to thank Miss H. Ainslie, Mr. H. Boyle, Mr. T. McFetters, Mr. E. Pinner, and Sisters A. Cook and M. J. Houston for their invaluable assistance during the course of these studies.

REFERENCES


COMMENTARY

During the course of our discussion at the workshop, Dr. McNeilly was asked to respond to certain points, and he has therefore contributed the following extra paragraphs.

Editor

A. S. McNeilly

Methods of Assessing Resumption of Ovarian Activity

Clearly, the only satisfactory method of assessing resumption of ovarian activity is a measure of the increase in oestrogen secretion. The increase in progesterone or pregnanediol, being products of the corpus luteum, occurs after ovulation, by which time conception and thus pregnancy could have occurred. It is possible that a measure of electrolyte changes using a dipstick for saliva or breast milk might be used, as there are indications of significant changes in electrolytes in the mid-follicular phase of the menstrual cycle (1).
More directly, a simple method for the measurement of oestrogen needs to be developed. In terms of chemical endpoints, a dipstick method could be developed which would measure an increase in oestrogens in blood, urine, or saliva. The latter two are the only practical body fluids for such a test. A simpler and equally appropriate method is the measurement of cervical mucus output as in the Billings method (2). The increase in mucus production is dependent on increasing amounts of oestrogen, and thus any increase in mucus in a breastfeeding women, who during lactational amenorrhoea often has very low oestrogen levels, would be potentially an excellent marker for the resumption of ovarian activity.

Comparative Aspects of the Role of Prolactin in the Suppression of Ovarian Activity

This is an immensely complex subject which has been reviewed recently (3). Studies in rats may be very misleading, in particular in terms of effects of prolactin and corpus luteum function, since no function will occur in the absence of high levels of prolactin, which in a woman would be indicative of pathological hyperprolactinaemia and amenorrhoea. Similarly, increases in prolactin induce an increase in dopamine turnover in the hypothalamus of the rat, mouse, and hamster. In the rat this is associated with a decrease in gonadotrophin secretion, whereas in mice and hamsters gonadotrophin secretion is enhanced. Finally, dairy cows, which are milked twice daily, return to oestrous between 30 and 90 days postpartum. If they are suckled by four calves, oestrous onset is delayed up to 300 or more days. In both cases, however, plasma levels of prolactin are the same. Thus, it is very difficult to rationalize the variable effects of prolactin to a single mechanism for the suppression of ovarian activity.


C. Robyn: Is the frequency as important as the duration of suckling in maintaining the lactational hyperprolactinaemia? Could animal data contribute to answer this question?

A. S. McNeilly: The principal suppressor of gonadotrophin secretion, apparently through suppression of the ability of the hypothalamus to generate and maintain pulsatile secretion of GnRH, is the suckling frequency. It appears that when suckling frequency is high, 10 to 20 times per day, then duration of each suckling episode is not very critical. However, when suckling frequencies decline to levels normal in the Western world, i.e., five to six times per day, then duration does become of importance. It is clear from our data that a decline in suckling duration alone is enough to trigger resumption of ovarian activity in the absence of a change in suckling frequency.

I do not believe animal studies will help unravel the relative importance of frequency and duration any better than more studies in different human cultural situations.

C. Robyn: Auditory, olfactory, and visual exteroceptive stimuli contribute to increased serum levels of prolactin in animals. I am not aware of data on the influences of these
stimuli on prolactin secretion in breastfeeding women. Would you please comment on the relative importance of nipple stimulation and exteroceptive stimuli?

A. S. McNeilly: It seems very probable that stimuli other than direct nipple stimulation are of very minor importance in influencing prolactin levels in lactation. In our own studies, exteroceptive stimuli such as the baby crying, which were potent in releasing oxytocin before suckling, did not affect prolactin at all (1).

C. Robyn: Why is there a gradual decline in basal levels of prolactin, although during the period of lactational amenorrhoea both suckling frequency and duration are maintained?

A. S. McNeilly: We do not know the reason for the gradual decline in basal levels of prolactin in the absence of any significant changes in suckling input.

C. Robyn: You find an apparently normal pulsatile LH secretion in 30% of the observation periods during lactational amenorrhoea. But how were these periods related to the suckling pattern? Do you have observations on long periods of time, such as 24 or 48 hr?

A. S. McNeilly: We do not have observations over a period longer than 7 hr. However, it is clear that when pulsatile secretion of LH occurs, this does result in follicle growth and increased oestrogen secretion. However, further pulsatile secretion of LH then appears to be inhibited by this rise in oestrogen, and the system switches off again. This is the basis of the hypothesis in Fig. 4 of our paper.

C. Robyn: Could you observe any changes in the LH pulsatility in relation to suckling: Do you have data on the urinary oestrogens in the lactating mothers with normal pulsatile LH secretion? Did these mothers recover ovulation earlier than those with an altered LH pulsatility?

A. S. McNeilly: We do not observe any change in LH pulsatility during suckling. Indeed, there is no significant change in FSH, although there is a slight decrease (~ 10%) in plasma levels of LH only at 15 min after the start of suckling. Thus, we have no evidence that suckling affects LH secretion acutely but is probably a more chronic suppression of secretion.

C. Robyn: You refer to two papers demonstrating decreased dopamine turnover in the tuberoinfundibular neurons (median eminence) during suckling in rats. Are you aware that several others showed just the opposite in lactating rats? (See Fuxe et al., ref. 45, C. Robyn et al., this volume). Is there any information available on dopamine concentration in the portal blood of rats during lactation or mammary stimulation?

A. S. McNeilly: I am aware of the other papers showing an apparent increase in dopamine turnover in the hypothalamus of suckling rats. However, Demarest et al. (2) discuss why their results are somewhat at variance with previous reports. Dopamine levels in portal blood have been measured and show a transient decline (3).

C. Robyn: You mention that the resumption of ovarian activity was independent of maternal body weight. Would you please comment further on this? Did you observe any significant changes in body weight index or fat stores during the lactational period?

A. S. McNeilly: We only weighed our women.

3. Plotsky PM, Neill JD. The decrease in hypothalamic dopamine secretion induced by suckling:
G. S. Masnick:

As a general observation I suggest that the literature on maternal nutrition, breastfeeding, and fertility, including the contributions prepared for this conference, has focused too much on levels and not enough on changes in levels. For example, the present paper by McNeilly et al. reiterates the rule of thumb for the minimum suckling frequency and total suckling duration necessary to suppress ovarian activity (more than 5 times and more than 65 min/day). Yet the authors also conclude that "rapid reduction in suckling or weaning, especially if occurring after prolonged lactation, can result in ovulation with normal luteal function, with the potential to carry a pregnancy if conception occurs." Presumably, rapid changes in suckling frequency, even if the above minimum frequency is maintained, could initiate the onset of ovulation.

P. G. Lunn and R. G. Whitehead:

It is rather difficult to write a critical assessment of this contribution, as the data presented, its interpretation, and the theories expressed are very closely aligned to our own view of the subject. In fact, we have frequently relied on the results of this group in the interpretation of our own observations in The Gambia. Instead, therefore, we will restrict our comments to a single discussion point, the importance of infertile menstrual cycles.

If lactational amenorrhea is to be used as a means of contraception either deliberately, as in industrialized societies, or tacitly, as in most developing countries, it is clearly important that some indication of the imminent return of fertility should be identified. The occurrence of infertile menstrual cycles and bleeds would seem to be an ideal natural warning sign that this protective mechanism is coming to an end. However, we are repeatedly told that the method is unreliable and that many women become pregnant during or shortly after lactation without ever experiencing a menstrual bleed. It is difficult to assess from the existing literature exactly how common it is for women to be fully fertile during their first cycle following lactational amenorrhea, and there is clearly considerable disagreement over the occurrence of ovulation during amenorrhea.

We would agree with McNeilly et al. that differences in breastfeeding practices probably explain much of the apparent variation in different reports. The finding by the Edinburgh group that mothers who reduce the number of breastfeeds slowly and initiate weaning...
gradually are most likely to experience a series of infertile cycles clearly fits with the endocrine data from The Gambia (1).

Concurrent serial analyses of the plasma concentrations of prolactin, oestradiol, and progesterone in lactating women indicated that below a critical value of plasma prolactin, plasma oestradiol concentrations rose (signalling the resumption of ovarian activity), but it was not until the prolactin concentration had fallen to a substantially lower value that progesterone levels climbed back towards normal, indicative of a full return of fecundity. The mean time taken for the plasma prolactin to fall from the upper to the lower “trigger” points was 14 to 15 weeks. Consequently, we would agree that the rate of fall in prolactin values, or perhaps more generally, the rate of decline of the suckling stimulus to the lactating mother may determine the number of infertile cycles or, if weaning is rather abrupt, whether they occur at all. If the mechanism does operate in this way, then clearly the message to mothers relying on this form of contraception is to introduce changes in feeding practices gradually so that full advantage can be taken of this warning sign.


H. L. Vis:

1. McNeilly does not tell us what number of day and night suckling periods is necessary to induce high basal levels of prolactin in relation to the age of the infant. It seems sufficient to have no more than five suckling episodes every 24 hours, provided that night feeding exists and that the total duration of feeding is more than 65 min/day. After several months of lactation it seems that the number of sucking episodes has to increase to more than 10 in order to maintain a high prolactin level.

Hennart (1) showed that variations in prolactin levels occur, when there are small changes in the suckling pattern (between 13 and 10 or 10 and 7 sucking episodes a day), but the variations are only of statistical significance after 1 year (Fig. C-I). The total duration of the sucking episodes when these are of high frequency are no longer of any importance (2).

Robyn et al. have made a suggestion in the present workshop about changes which may occur in the sensitivity of the hypothalamic releasing mechanism. We do not know if malnutrition changes the sensitivity of the suckling reflex. Yet there are indications in the literature (3) that undernutrition, exercise, and stress do induce hormonal patterns suggestive of hypothalamic changes. But even if the nutritional status of the mother should enhance the influence of the normal impulses from the nipple, still the threshold of the frequency of suckling per day, to maintain high levels of prolactin, remains elevated after 1 year of lactation.

2. We must pay attention to the difference between the meaning of the expression “supplementary food” and true “weaning food.” Weaning foods or breastmilk substitutes may decrease the frequency of breast feeding. In developing countries, however, when
FIG. C-1. Prolactin levels in relation to suckling frequency: (○)more than 10 times a day; (●)less than 7 times a day. The differences in prolactin levels are significant after only 1 year of lactation (Hennart, 1983).

FIG. C-2. Basal prolactin levels in urban and rural areas in mothers who exclusively breastfeed and in those who add supplementary food. (Hennart, 1983.)
lactating mothers are undernourished and even though the number of breastfeeds is elevated, the milk production will be limited (4). The mothers are forced to introduce supplementary food (bananas, cassava) after every breastfeed. Under these circumstances the number of suckling episodes will not diminish, nor will the milk production or the prolactin level (Fig. C-2) at least during the first 6 months of lactation.


R. E. FRISCH:

The hormonal control of the lactation process is clearly presented. However, the point of view that only the suckling pattern controls the length of lactational amenorrhoea results in many statements and conclusions which are not supported by existing data or are as yet undetermined for populations differing from the sample studied by the authors. I will now list these statements.

1. I believe that the length of the period of lactational amenorrhoea and the menstruation-pregnancy interval “will vary considerably depending” not only on the pattern of breast-feeding but on the nutritional state of the mother and other unknown factors.
2. Following parturition, you report that plasma levels of FSH and LH “increase within 30 days in a non-breastfeeding woman.” This may be so in the population studied but not necessarily in that time period in poorly nourished women (1).
3. “... similar longitudinal studies in other societies must be undertaken to determine the parameters necessary for maintenance of lactational amenorrhoea.” This presumes that it can be maintained. However, there is no evidence that it is biologically possible to do so after some time point which probably differs in different societies.
4. How does a mother maintain night feeding to prolong amenorrhoea if the infant has developed neurologically and physically to the stage where he or she does not wake up for night feeding?
5. Interestingly, amenorrhoeic athletes and dancers and underweight women also have low oestrogens and low gonadotrophins, associated with hypothalamic dysfunction (2,3). This suggests that raised prolactin levels may be related not only to the suckling stimulus, but to other signals from the higher levels of the central nervous system which control energy metabolism or maintenance of adiposity etc.
6. What is meant by the pattern of suckling during each suckling episode being important in releasing prolactin and suppressing gonadotrophin release?
7. Under the heading "Resumption of Ovarian Activity," what were the weights for height of each of the women when ovarian activity resumed? Weight alone tells you nothing about the relative leanness (or fatness) which other data indicate may be one of the factors interacting with the suckling stimulus. [See, for example, animal data cited by Sadlier (4) on differences in length of lactational amenorrhoea of sheep and rats depending on the quantity and quality of the food supply and the "condition" of the female when mated]. Similar data are available for cattle.

8. Under the heading "Ovulation and Pregnancy During Amenorrhoea," differences in frequency of ovulation in the cycle before the end of lactational amenorrhoea would be expected if the nutritional state of the mother and her infant interact with the suckling pattern. As stated, the question becomes, What determines the different suckling patterns of the population studied?

9. That continuation of night feeds might delay the onset of ovulation is very plausible. However, the interesting question then becomes, What are the characteristics of the infants and mothers who continue night feeding at a particular time postpartum? Age of mother? Parity? Length of birth interval? Weight for height? Weight of infant?

10. Interestingly, women who were underweight and gained sufficient weight to begin cycling often have cycles with a short luteal phase. We also observed a short luteal phase in athletes before they became amenorrhoeic or anovulatory with intensive exercise or on resumption of cycling (5,6). These observations may be pertinent because they are associated with changes in energy metabolism and storage.

11. As above, how do you "maintain night feeds with only token suckling during the day"?

12. Under "Conclusions": There is no doubt that breastfeeding "will suppress fertility for a considerable period of time (up to 75 weeks) even in an industrialized well-nourished population." There is also no doubt that the period can be as short as 12 weeks for women who are breastfeeding on demand and not supplementing the breastmilk (Salber et al., 1966, and personal data). As above, what distinguishes these women and their infants from those who do not resume cycling?

13. To the statement "It is clear that the maintenance of infertility during breastfeeding is directly dependent on the strength of the suckling stimulus" I would add: plus other factors such as the present and past nutritional status of the mother, her age, and parity, as pointed out above.

What determines the "strength of the suckling stimulus"? Weight and age of the infant? Maternal factors above?


K. PREMA RAMACHANDRAN:

It is worth stressing that the endocrine profile described pertains to well-nourished women in developed countries with their characteristic breastfeeding patterns. The mechanisms of endocrine control of lactational infertility in women with different patterns of breastfeeding (e.g., on-demand frequent feeds, repeated night suckling) are not yet clearly understood. Demonstrated differences in endocrine profile between women in developed and developing countries might be partly due to differences in the breastfeeding pattern and partly due to difference in nutritional status. It is difficult to isolate the effects of one from the other because in natural situations they coexist.

Some of the data from developing countries show that the number of suckling episodes and the introduction of supplements do have an impact on plasma prolactin levels, even in situations where women breastfeed their infants 10 to 15 times a day.

J. DOBBING

Application of the Edinburgh Findings on the Effects of Supplementary Feeds on Lactational Infertility

These findings have often been uncritically extrapolated to impoverished communities in developing countries and an attempt made to suggest that supplementation even of underfed babies risks inhibiting breastfeeding. I think it important to reiterate that such an extrapolation has never been made or implied by the authors directly concerned, who have stated that they consequently deplore such uncritical conclusions. There is good evidence, especially from the Belgian workers in Kivu, that no inhibition or shortening of the duration of breastfeeding occurs due to underfed, suckling babies being relieved of their hunger by suitable and desperately needed supplements.