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ENDOCRINE ASPECTS OF LACTATION AND POSTPARTUM INFERTILITY

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During pregnancy, the breast is capable of milk secretion beginning sometimes in the midtrimester of gestation; however, the secretion of mature milk is considered complete by 1 week post-delivery. The production of milk or lactogenesis is apparently initiated by the postpartum decline in estrogen and progesterone placental production, when the placenta is delivered and the source of these hormones is removed [1–3]. Progesterone and estrogens disappear gradually and require approximately 1 week after delivery to reach the levels found in the nonpregnant woman. Maternal prolactin secretion exhibits important variations during pregnancy and puerperium. Prolactin production, which increases gradually during gestation, shows a fall following delivery, and the rate of decrease in basal levels is slow and depends on the amount of suckling by the infant (Fig. 1). The number of lactotroph cells also increases in relation to the duration of pregnancy. Prolactin production is essential for the onset of lactation in humans, inducing milk synthesis and secretion by the alveolar cells of the breasts. The use of inhibiting prolactin-secretion drugs, such as bromocriptine, are effective to suppress puerperal lactation [4, 5]. However, high levels of prolactin are not necessary for lactogenesis since milk production occurs in some lactating women with low levels of prolactin as well as in women who have been given bromocriptine [6, 7]. It has been established that lactation is regulated by prolactin, oxytocin, and local factors as well as neural reflexes; though removal of milk from the breast at regular intervals is necessary for maintenance of lactation [8]. Both prolactin and oxytocin are released in response to breast-feeding; thus prolactin acts on the mammary epithelial cells to induce the production of milk, and oxytocin acting on the mioepithelial cells facilitates milk removal by causing ejection of milk from the alveoli into the ducts [8]. Lactation stops when suckling by the infant is absent and milk is not removed from the breast. Prolactin induces an increase in the number of receptor binding sites and enters the alveolar cells. Within the cells, prolactin attaches to the Golgi apparatus and provokes the synthesis of casein, lactose, and alpha-lactalbumin. In all mammals prolactin is the major hormonal trigger in the initiation of lactation. Suckling stimuli is so relevant that it is able to overcome the inhibitory effect of prolactin-blocking drugs [6].

LACTATION

Suckling initiates afferent impulses which travel to the brain via the sensory nerves from the nipples and eventually bring about the secretion of both prolactin and oxytocin. Suckling leads to a surge of prolactin secretion and persists shortly after the infant ceases to suckle. It is accepted that only that part released in the first few minutes of suckling is required for milk secretion. Thus prolactin released

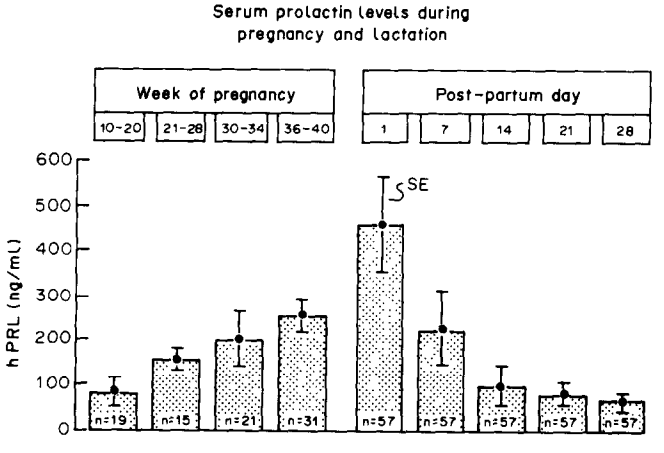

Fig. 1. Prolactin (hPRL) levels in maternal blood increase through gestation, showing a sharp fall immediately after delivery regardless of lactation [Soria *et al.*, *Ann. Endocr.* **38** (1977) 55.

during one episode of suckling is used to stimulate milk production for the next episode. The amount of milk secreted is matched to the demands of the infant and prolactin seems to be the linkage between the amount of milk secreted and the intensity of breast feeding. In support of this theory is the observation that bromocriptine inhibits both prolactin secretion and milk production [4, 5]. In late pregnancy, human placental lactogen levels in blood are around 100 times higher than those of prolactin. Placental lactogen disappears immediately following delivery. The role of placental lactogen is to initiate changes in the alveoli rather to induce milk secretion. Another observation is that increasing prolactin production by the administration of TRH (thyrotropic-releasing hormone), which induces secretion of both TSH and PRL, (Fig. 2) or metoclopramide (Fig. 3), improves lactation in women with low milk production [9–12]. On the other hand, some investigators have been unable to demonstrate any relation between prolactin concentrations and milk yield [13, 14]. Another observation is that prolactin secretion is relatively low in late lactation even when milk production is maintained at high levels [14, 15]. Based on these observations, it may be concluded that prolactin secretion is necessary to initiate and maintain early lactation, but the actual amount of milk production may be regulated by additional factors. Other mechanisms such as the amount of milk remaining in the alveolar spaces after feeding may play an important role; therefore lactation is influenced by the frequency of nursing episodes and the duration of suckling per day. Frequent nursing is required to maintain the pituitary responsiveness to the suckling stimulus at an optimal level. It was already mentioned that as a result of expulsion of placenta and consequently removal of the great levels of estrogens and progesterone, the blockade of prolactin binding

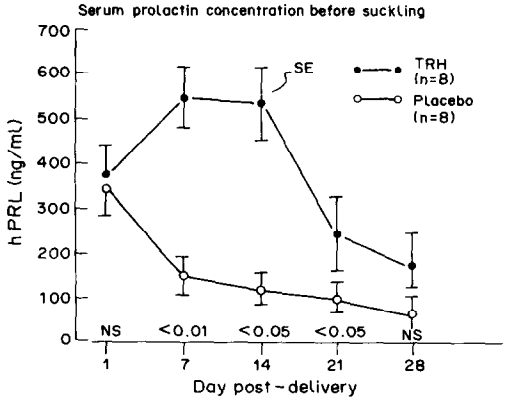

Fig. 2. Serum prolactin (hPRL) values in patients who received thyrotropin-releasing hormone (TRH) in order to increase prolactin secretion (●) and control women (○). Levels of hPRL decline progressively in lactating women in contrast with the elevated hPRL levels of women receiving TRH. All samples were obtained immediately before breast-feeding. [Zárate *et al.*, *J. clin. Endocr. Metab.* **43** (1976) 301].

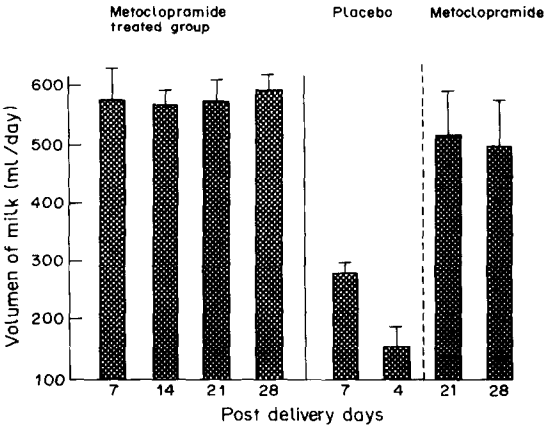

Fig. 3. Volume of milk in puerperal patients with defective lactation. The patients treated with metoclopramide starting in the immediate postpartum period had normal lactation. In contrast, those women who received the placebo had a progressive diminution of milk production; however, as soon as these patients were given metoclopramide there was an increase in milk yield [Guzmán *et al.*, *Acta obstet. Gynec. Scand.* **58** (1979) 53].

sites on the alveolar cells is removed and prolactin enters the cells, converting the presecretory cells into secretory cells which synthesize casein in increasing amounts, and milk is accumulated into the lumen of the acini as colostrum. Colostrum differs from mature milk in that it contains more protein, less fat, and less lactose. It is well known that breast-feeding as early as possible after delivery is beneficial in establishing lactation.

POSTPARTUM INFERTILITY

The period of lactation is associated with considerable alterations of the endocrine system of the nursing mother. The high prolactin levels accompanying lactation are responsible for ovarian activity suppression, rendering women infertile for 6–8 weeks after the birth of an infant [16–18]. The mechanism of this ovarian inactivity during lactation has been studied widely and is the subject of controversy. Immediately following delivery, high prolactin levels coincide with low levels of both LH and FSH (Fig. 4). Serum FSH is undetectable during the first week post-partum; thereafter. there is an increase in FSH levels which reach a maximum by the third week post-partum (Fig. 5). These FSH levels are higher in lactating women than in women who have received bromocriptine in order to suppress prolactin secretion and milk production (Fig. 6). Serum estradiol remains low throughout the first 4 weeks postpartum, showing no difference between lactating and non-lactating women. Studies carried out with the use of synthetic LHRH to induce pituitary gonadotropin response during puerperium have demonstrated that LHRH administration fails to obtain FSH secretion (Fig. 7). On day 15 postpartum, baseline levels of FSH are found within

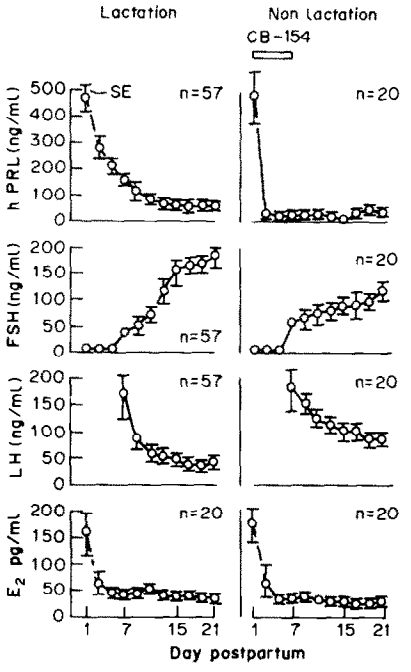

Fig. 4. Serum prolactin (hPRL), gonadotropins (FSH and LH) and estradiol (E_2) levels in lactating women and bromocriptine (CB-154) treated puerperal women. PRL levels of lactating women declined after delivery. In the treated group, PRL concentrations were effectively suppressed by CB-154. FSH was undetectable during the first week postpartum in all women. Thereafter, they showed increasing FSH levels which were higher in lactating women than in the treated group. In contrast, LH levels were higher in those women receiving CB-154. Estradiol decreased and remained at low levels in the two groups [Villalobos *et al.*, *Acta endocr., Copenh.* **83** (1976) 236.

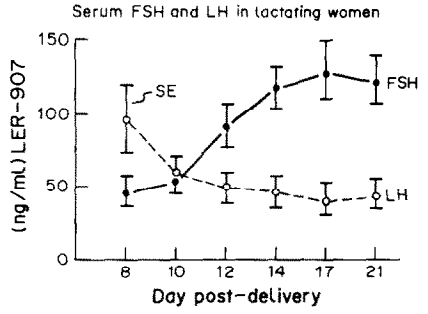

Fig. 5. Serum gonadotropins (FSH/LH) levels in lactating women. Different dynamics of the two hormones are observed. FSH (●) levels increase steadily, reaching the maximum concentration by the third week, while LH (○) remained at very low levels. (Villalobos *et al.*, 1976).

normal limits and LH concentration is below normal as compared with the follicular phase values of the menstrual cycle [19, 20]. It is also observed that FSH release in response to LHRH is greater and LH release is diminished when compared with that observed in normal menstruating women [20, 21]. Therefore the recovery of pituitary function following delivery is faster for FSH than for LH, and 15 days after delivery a reversal from menstruating women on the FSH/LH secretory responsiveness to LHRH is observed [20, 21]. In spite of the high levels of FSH, circulating estrogens remain characteristically low as long as prolactin levels are elevated. The decline in serum prolactin to normal non-pregnant levels is associated with a progressive increase in serum estradiol which is followed by rising LH levels and ovulation. When prolactin secretion is suppressed by bromocriptine, ovarian estrogen secretion is normalized and a surge of LH and FSH is observed. Puerperal hyperprolactinemia also influences the normal episodic release of LHRH and subsequently the rhythmic pulses of FSH and LH secretion necessary for appropriate ovarian stimulation [22, 23]. The ovarian responsiveness to gonadotropic stimulation is suppressed during lactation and it is believed that high circulating levels of prolactin are responsible for this phenomenon. The responsiveness of the hypothalamic–pituitary system to the positive effects of estrogens is also suppressed in the immediate puerperium (Fig. 8). Administration of estradiol to lactating women is not followed by FSH release [24, 25]. The neurogenic-hormonal response to suckling includes the release

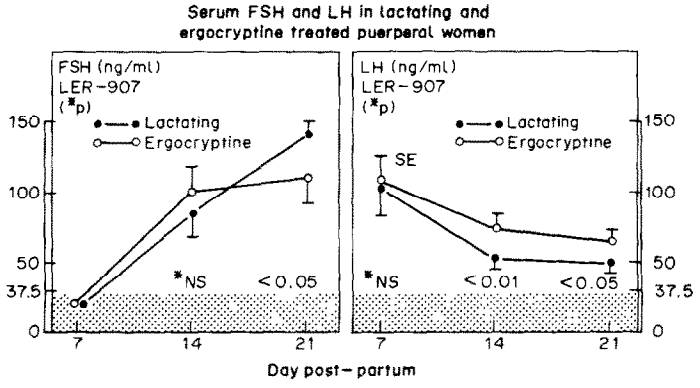

Fig. 6. Serum gonadotropins (FSH/LH) levels in lactating women (●) and ergocriptine-treated puerperal women (○). FSH levels are higher in lactating women than in ergocriptine-treated group at the third week. In contrast, LH levels are higher in the treated group since the second week (Villalobos *et al.*, 1976).

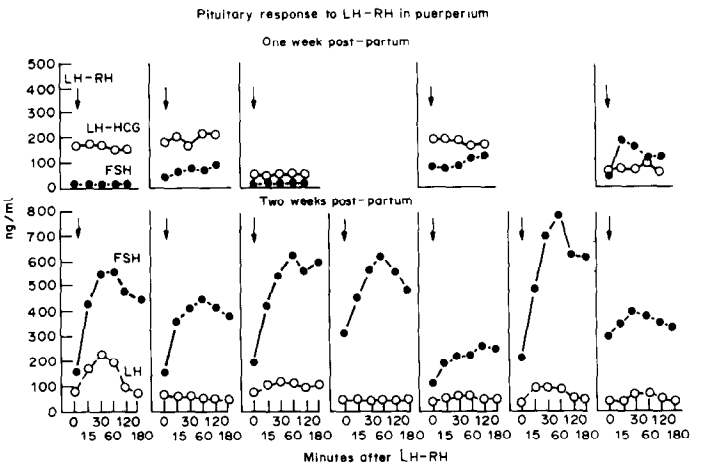

Fig. 7. Serum gonadotropins (LH-HCG/FSH) concentration before and after 250 μg i.v. synthetic luteinizing hormone-releasing hormone (LH-RH) to women 2 weeks after delivery. The recovery of pituitary functions if faster for FSH (●) than for LH (○) [Canales *et al.*, *J. clin. Endocr. Metab.* **38** (1974) 1140].

of pituitary prolactin, and, it was also assumed, the simultaneous inhibition of gonadotropin release [26]. More recent studies [27] have shown data supporting the view that pituitary gonadotropin secretion is not inhibited by suckling (Fig. 9). It is concluded that postpartum infertility depends on the duration of lactation, and prolactin production plays a relevant function in this mechanism. Prolactin appears to act at various levels: (1) direct effect on LHRH-gonadotropin releasing mechanism, (2) inhibition of pulsatile FSH/LH secretion, (3) suppression of the positive feedback effects of estrogens, (4) direct interference with ovarian steroidogenesis, and (5) inducing some degree of ovarian refractoriness to gonadotropic stimulation.

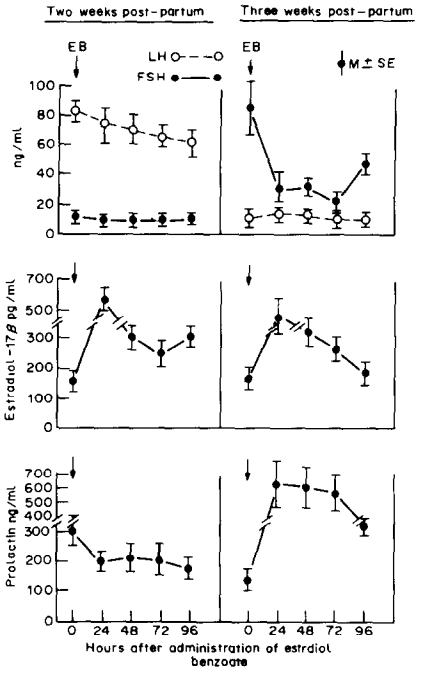

Fig. 8. Gonadotropins (FSH/LH), prolactin and estradiol concentrations in lactating women treated with estradiol benzoate (EB) at two intervals puerperium. It is observed that the responsiveness of the hypothalamic–pituitary system is suppressed during the first puerperal week. The responsiveness of FSH (●) but not of LH (○) at the third week after delivery indicates that the recovery of pituitary function is faster for FSH than for LH. PRL responsiveness is apparent from the third post-delivery week [Canales *et al.*, *Int. J. Gynec. Obstet.* **19** (1981) 79].

STIMULATION OF MILK PRODUCTION

Initiation of milk secretion in the human is closely related to the prolactin release induced by a normal infant's suckling [28, 29]. Conversely, defective

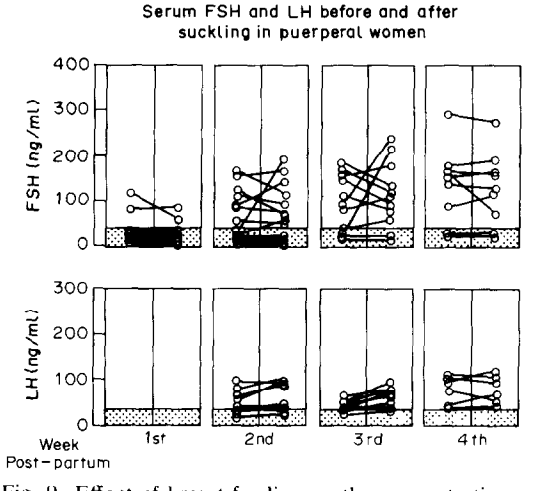

Fig. 9. Effect of breast-feeding on the concentrations of gonadotropins (FSH/LH) in puerperal women. Dashed areas represent the undetectable range of gonadotropins. It is observed that FSH/LH secretion is not inhibited by suckling [Soria *et al.*, *Neuroendocrinology* **20** (1976) 43].

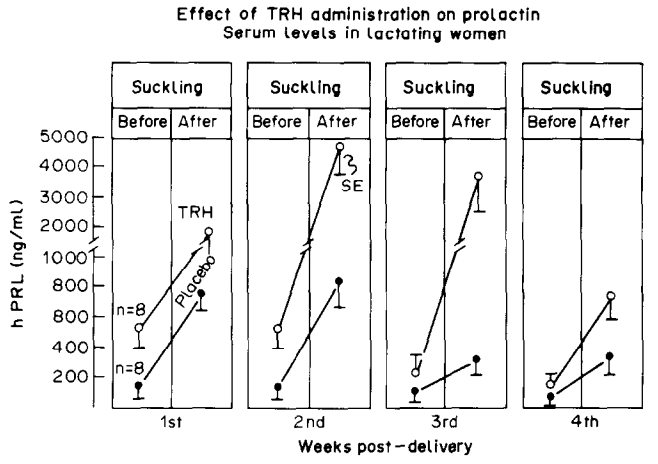

Fig. 10. Serum prolactin (hPRL) levels in lactating women receiving thyrotropin releasing hormone (TRH) or placebo. PRL was measured before and 30 min after infant's nursing. The highest PRL levels were observed in the first postpartum week. Beyond the second week, basal PRL levels were still elevated compared with those of the controls [Zárate *et al.*, *J. clin. Endocr. Metab.* **43** (1976) 301].

lactation has been associated with a defective prolactin secretion in response to impaired suckling [29]. On the basis of these observations it has been proposed that milk production might be augmented by the use of pharmacological agents which induce an increase in prolactin secretion [30–32]. Thus defective lactation associated with prolactipenia can be treated by the manipulation of prolactin secretion through the administration of drugs which enhance prolactin release. Puerperal women with a past history of defective lactation and prolactin levels under the normal range have been treated successfully with metoclopramide and TRH (Fig. 10). This treatment induces persistently elevated basal levels of prolactin and good milk production. In cases with full lactation, the pharmacological enhancement of prolactin secretion may not have an additive effect on milk production [33].

Bromocriptine and TRH have been shown to possess opposite effects, inhibitory and stimulatory,

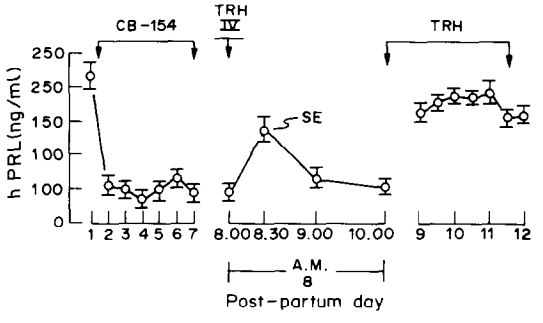

Fig. 11. Effect of sequential treatment of bromocriptine (CB-154 and thyrotropin-releasing hormone (TRH) on serum prolactin (hPRL) levels. PRL levels remained very low when patients were receiving bromocriptine. Intravenous TRH (250 μg) elicited a significant rise in hPRL concentrations within 30 min. Oral TRH (20 mg, 4 times a day) continued to stimulate the PRL release [Canales *et al.*, *Am. J. obstet. Gynec.* **128** (1977) 695].

respectively, on prolactin secretion and subsequently on lactation [34]. Taking into account this concept, pituitary prolactin secretion as well as puerperal lactation has been manipulated by the administration of pharmacologic agents (Fig. 11).

From the above considerations, lactation is effectively induced by a regular suckling stimulus associated with the administration of pharmacological agents in puerperal women. In addition, it is possible to induce lactation in adoptive nulliparous women when they are well prepared through nipple stimulation before and after the infant's arrival and with the administration of drugs which induce prolactin secretion [35].

CONCLUSION

Tremendous progress has been achieved in understanding the hormonal interactions that regulate lactation. Although some problems remain for further studies, the most relevant are related to improving breast-feeding performance and better knowledge of the mechanisms by which lactation influences fertility during puerperium.

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REFERENCES

1. Bruce J. O. and Ramírez V. D.: Site of action of the inhibitory effect of estrogen upon lactation. *Neuroendocrinology* **6** (1970) 19.
2. Turkington R. W. and Hill R. L.: Lactose synthetose progesterone inhibition of the induction of β-lactalbumin. *Science* **163** (1969) 1458.
3. Neifert M. R., McDonough S. L. and Neville M. C.: Failure of lactogenesis associated with placental retention. *Am. J. obstet. Gynec.* **140** (1981) 477.
4. Del Pozo E., Broun de Re R., Varga L. and Friesen H. G.: The inhibition of prolactin secretion in man by

CB-154 (2-Br-alpha-ergocriptine). *J. clin. Endocr. Metab.* **35** (1972) 768.
5. Canales E. S., Levison G., González-Colindres J., Ortíz de la Peña R. and Zárate A.: Utilidad de la bromo-ergocriptina en la inhibición de la lactancia fisiológica. *Ginec. Obstet. Mex.* **37** (1975) 49.
6. Zárate A., Canales E. S. and Alger M.: The effect of pregnancy and lactation on pituitary prolactin secreting tumors. *Acta endocr., Copenh.* **92** (1979) 407.
7. Howie P. W., McNeilly A. S., McArdle T., Smart L. and Houston M.: The relationship between suckling-induced prolactin response and lactogenesis. *J. clin. Endocr. Metab.* **50** (1980) 670.
8. Grosvenor C. E. and Mena G.: Neural and hormonal control of milk secretion and milk ejection. In *Lactation* (Edited by B. L. Larsen and V. R. Smith). Academic Press, New York, Vol. 2 (1974) p. 227.
9. Tyson J. E., Perez A. and Zanurtu J.: Human lactational response to oral thryotropin releasing hormone. *J. clin. Endocr. Metab.* **43** (1976) 760.
10. Guzmán V., Toscano G., Canales E. S. and Zárate A.: Improvement of defective lactation by using oral metoclopramide. *Acta obstet. Gynec. Scand.* **58** (1979) 53.
11. Kauppila A., Kivinen S. and Ylikorkala O.: Metoclopramide increases prolactin release and milk secretion in puerperium without stimulating the secretion of thryotropin and thryroid hormones. *J. clin. Endocr. Metab.* **52** (1981) 436.
12. Kauppila A., Kivinen S. and Ylikorkala O.: A dose response relation between improved lactation and metoclopramide. *Lancet* **1** (1981) 1175.
13. Martin R. H.: The place of PRL in human lactation. *Clin. Endocr.* **18** (1983) 295.
14. Glasier A., McNeilly A. S. and Howie P. W.: The prolactin response to suckling. *Clin. Endocr.* **21** (1984) 109.
15. Delvoye P., Demaegd M., Uwayitu-Nyampeta and Robin C.: Serum prolactin, gonadotropins and estradiol in menstruating and amenorrheic mothers during two years lactation. *Am. J. obstet. Gynec.* **130** (1978) 635.
16. Zárate A., Canales E. S., Soria J., Ruiz F. and MacGregor C.: Ovarian refractoriness during lactation in women: effect of gonadotropin stimulation. *Am. J. obstet. Gynec.* **112** (1972) 1130.
17. Reyes F. I., Winter J. S. D. and Faiman C.: Pituitary–ovarian interrelationships during the puerperium. *Am. J. obstet. Gynec.* **114** (1972) 589.
18. Zárate A., Canales E. S., Soria J., León C., Garrido J. and Fonseca E.: Refractory postpartum ovarian response to gonadal stimulation in nonlactating women. *Obstet. Gynec.* **44** (1974) 819.
19. Canales E. S., Zárate A., Garrido J., León C., Soria J. and Schally A. V.: Study on the recovery of pituitary FSH function during puerperium using synthetic LRH. *J. clin. Endocr. Metab.* **38** (1974) 1140.
20. Jeppsson S., Rannevik G. and Kullander S.: Studies on the decreased gonadotropin response after administration of LH/FSH-releasing hormone during pregnancy and the puerperium. *Am. J. obstet. Gynec.* **120** (1974) 1029.
21. Villalobos H., Canales E. S., Zárate A., Soria J. and McGregor C.: Effect of prolactin suppression on gonadotrophic secretion in the puerperium. *Acta endocr., Copenh.* **83** (1976) 236.
22. Rolland R., DeJong F. H., Schellenkens L. A. and Lequin R.: The role of prolactin in the restoration of ovarian function during the early post-partum period in the human female. *Clin. Endocr.* **4** (1975) 27.
23. Ishizuka B., Quigley M. E. and Yen S. S.: Postpartum hypogonadotrophinism: evidence for increased opioid inhibition. *Clin Endocr.* **20** (1984) 573.
24. Canales E. S., Fonseca M. E., Mason M. and Zárate A.: Feedback effect of estradiol on follicle-stimulating hormone and prolactin secretion during puerperium. *Int. J. Gynaec.* **19** (1982) 79.
25. Crystle C. D., Sawaya G. A. and Stevens V. C.: Effects of ethinyl estradiol on the secretion of gonadotropins and estrogens in postpartum women. *Am. J. obstet. Gynec.* **116** (1973) 616.
26. Minaguchi H. and Meites J.: Effect of suckling on hypothalamic LH-releasing factor and prolactin inhibiting factor, and on pituitary LH and prolactin. *Endocrinology* **80** (1967) 603.
27. Soria J., Zárate A., Canales E. S. and Villalobos H.: Effect of suckling on serum follicle-stimulating hormone and luteinizing hormone in nursing women. *Neuroendocrinology* **20** (1976) 43.
28. Aono T., Shioji T., Shoda T. and Kurachi K.: The initiation of human lactation and prolactin response to suckling. *J. clin. Endocr. Metab.* **44** (1977) 1101.
29. Archer D. F., Nankin H. R., Gabos P. F., Maroom J., Nosetz S., Wadhwa S. R. and Josimovich J. B.: Serum prolactin in patients with inappropriate lactation. *Am. J. obstet. Gynec.* **119** (1974) 466.
30. Aono T., Shioji T., Aky T., Hirota K., Nomura A. and Kurachi K.: Augmentation of puerperal lactation by oral administration of sulpiride. *J. clin. Endocr. Metab.* **48** (1979) 478.
31. De Gezelle H., Ooghe W., Thiery M. and Dhont M.: Metoclopramide and breast milk. *Eur. J. obstet. Gynec. reprod. Biol.* **15** (1983) 31.
32. Kauppila A., Anunti P., Kivinen S., Koivisto M. and Ruokonen A.: Metoclopramide and breast feeding: efficacy and anterior pituitary responses of the mother and the child. *Eur. J. obstet. Gynec. reprod. Biol.* **19** (1985) 19.
33. Zárate A., Villalobos H., Canales E. S., Soria J., Arcovedo F. and McGregor C.: The effect of oral administration of thyrotropin-releasing hormone on lactation. *J. clin. Endocr. Metab.* **43** (1976) 301.
34. Canales E. S., Lasso P., Murrieta S., Fonseca E., Soria J. and Zárate A.: Feasibility of suppressing and reinitiating lactation in women with premature infants. *Am. J. obstet. Gynec.* **128** (1977) 695.
35. Auerback K. G. and Avery J. L.: Induced lactation: a study of adoptive nursing by 240 women. *Am. J. Dis. Childh.* **135** (1981) 340.