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# THE ROLE OF PROLACTIN IN HUMAN REPRODUCTION

by

RAMA VAIDYA, M.D.

and

ANIL SHETH, Ph.D.

*Introduction—History*

The earliest recognition that anterior pituitary has an action of initiating lactation in the mammary gland came in 1928-29 with the work of Stricker and Grueter (1928) on rabbits treated with anterior pituitary extracts. This finding was further elaborately developed in the species like rat by Evans and Simpson (1929) and by Corner (1930). A very fascinating account of the comparative physiology and the probable evolutionary development of the prolactin molecule has been given by Bern and Nicoll (1968). The development of specific and sensitive radioimmunoassay for prolactin greatly encouraged the investigative efforts in the basic and applied aspects of prolactin action and control. The presence of human prolactin as a separate entity from human growth hormone was speculated for long on the basis of clinical observations, however, the proof of its existence was convincingly demonstrated only in the late sixties and early seventies. The availability of radioimmunoassay for prolactin, development of new drugs that effectively control prolactin secretion and increasing knowledge and understanding of neuroendocrinology in general have been several of the factors that have contributed to the resurgence of world wide interest in the subject.

Certain clinical observations greatly enhanced the understanding of the control mechanism of prolactin secretion in human. The occurrence of galactorrhea coupled with Parkinsonism in a patient on α-methyldopa (Vaidya *et al* 1970), the role of L-DOPA in the control of prolactin secretion (Turkington, 1972) and the observation of increase in prolactin by thyrotropin releasing hormone (Jacobs *et al* 1971) are some of these.

Galactorrhea has assumed a different significance in gynaecological practice. On one hand, the magnitude of the pro-

*Institute for Research in Reproduction (ICMR), Jehangir Merwanji Street, Parel, Bombay 400 012, India.*

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blem is increasing because of drug-induced galactorrhea. On the other hand, the diagnosis of underlying pituitary tumor continues to be a great clinical challenge.

The aforesaid areas relate to the familiar aspects of mammogenic or lactogenic function of prolactin. However, the demonstration of prolactin in human semen (Sheth *et al* 1975) and cervical mucus (Sheth *et al* 1976) have opened up relatively new areas for investigating the role of prolactin in human reproduction.

The present review is oriented to the basic aspects of prolactin physiology and pathophysiology that provide rationale and understanding (1) to clinical problems of normal and abnormal lactation, (2) to investigative approach and diagnostic categorization of these disorders.

*Chemistry*

The primary structure of prolactin has been determined following the extensive studies carried out by Li and his colleagues on the extraction and purification of prolactin from various species (Li *et al* 1941, 1942, 1969, 1972). Unlike gonadotropins (LH and FSH) which are glycoproteins, prolactin is a single polypeptide chain of 200 amino acids without carbohydrate attachment. Its primary structure is different from that of human growth hormone, and hence there is little if any immunological cross reaction between prolactin and growth hormone.

*Assay Methods*

None of the bioassays are sensitive and practical to determine prolactin levels in serum samples. Recent development of radioimmunoassays as well as radioreceptor assays have made it possible to investigate the levels of this hormone in various physiological and pathological conditions.

Both heterologous and homologous radioimmunoassays have been developed for measuring prolactin in body fluids (Friesen *et al* 1973, Cole and Boyns 1973, Robyn *et al* 1973). These assays are sensitive as well as specific. Prolactin could be measured in as little as 100 $\mu$l of serum sample without any pretreatment. At present reagents for determining prolactin by radioimmunoassay are distributed to qualified investigators by National Pituitary Agency, NIH, USA.

In certain clinical disorders, it has been noticed that the prolactin values obtained by bioassays and immunoassays do not agree. This discrepancy could be due to inability of immunoassay to differentiate between biologically active and inactive hormones. To overcome these difficulties radio-receptor assays have been developed recently.

Radioreceptor assays which are quicker (only 3 to 4 hours as compared to 48-72 hours for radioimmunoassays) and more related to biological potency of a hormone have been developed for prolactin (Frantz *et al* 1974, Shiu and Friesen 1974). Specific receptors are isolated either from pregnant rabbit mammary gland or rat liver. The binding of labelled prolactin to the receptor forms the basis of this assay. The sensitivity and the specificity of the assays are comparable to radioimmunoassays and no doubt that in very near future these assays will come in wider use for clinical research.

*Physiology*: (a) *Secretion*: Prolactin is secreted by anterior pituitary cells known as lactotrophs. Lactotrophs are usually, not identifiable in pituitaries of infants, males or non-pregnant female

(Vorherr, 1974). But they increase in number and size during pregnancy and are known as "Pregnancy cells". Secretory granules are seen in acidophilic lactotrophs by midpregnancy. Near term lactotrophs almost fill up 50% of all epithelial cells of pars distalis.

Native human prolactin from the pituitary gland, amniotic fluid and from semen is heterogenous (Hwang *et al* 1973; Ben-David and Charambach 1974; Rogol and Charambach, 1975; Dattatreyamurty and Sheth, 1977). There is "little" and "big" (20%) components of circulating prolactin in situations with high secretion rate of prolactin such as during pregnancy and pituitary tumours. A large proportion of big forms may be found in circulation (Shiu and Friesen, 1974). It has been found by radioreceptor assays that "big-big" forms of prolactin may be biologically inactive. This may explain the absence of galactorrhea in the presence of hyperprolactinemia.

Experimental evidence suggests that prolactin is transported in blood as the free molecule. Very little is known about the metabolism of prolactin but the inactivation of prolactin seems to be very rapid. The half life of hPr is estimated to be between 15-43 minutes.

(b) *Target Sites and Mechanism of Action*

A current view of the molecular basis of hormone action is that receptors are present in target tissues that bind specifically to a hormone, and this initiates a series of intracellular events which induce changes in cell growth and function. Specific binding receptors of prolactin have been reported in mammary gland, liver, kidney, ovary, gonads, ventral prostate and seminal vesicles (Rajamiens *et al* 1974, Friesen 1973, Frantz *et al* 1974).

Prolactin effects on the prostate and spermatozoa may involve the generation of cyclic AMP (Boyns *et al* 1972, Shah *et al* 1976). In the mammary gland, in contrast, it does not stimulate cyclic AMP synthesis, but induces protein-kinase enzymes with which cyclic AMP interacts (Turkington *et al* 1973).

(c) *Hypothalamic Control*

The hypothalamic control of prolactin secretion unlike other pituitary tropic hormone is predominently inhibitory in nature. The nature of prolactin inhibitory factor (PIF) is not yet known. There also seems to be a hypothalamic prolactin releasing factor (PRF) which stimulates prolactin synthesis and release. This dual hypothalamic control of pituitary prolactin secretion by PIF and PRF is regulated by neurotoransmitters dopamine and serotonin (Meites 1973): The concentration of these compounds is greater in hypothalamus than in rest of the brain. They serve as a link between neural cells of hypothalamus and hormone (e.g. PIF) secreting cells of hypothalamus. Thyroid releasing hormone causes release of prolactin in human (Jacobs *et al* 1971, Bowers *et al* 1973). Drugs like L-DOPA, that elevate functional pool of dopamine in hypothalamus, increase PIF and thus inhibits prolactin secretion in animals or humans with intact hypothalamo-pituitary unit. On the other hand, chronic intake of drugs like chlorpromazine and other phenothiazines, alpha-methyldopa, reserpine etc. elevate prolactin (Shulman *et al* 1973) and may cause galactorrhea (Gordon and Circurel 1969). This is believed to be due to decrease in hypothalamic secretion of PIF ascribed to be due to decrease in effective hypothalamic dopamine levels.

(d) *Serum Prolactin Levels in Health and Disease*

Basal serum prolactin levels show random fluctuations and hence normal values have wide range. Prolactin levels are elevated at night and related to sleep (Nokin *et al* 1971). Day time naps also result in elevation of prolactin levels. Serum prolactin levels in boys and girls, adult males and females as well as during normal menstrual cycle, pregnancy and postpartum period are shown in Table I.

TABLE I

*Serum Prolactin Levels in Different Physiological Conditions*

| | Groups | Total No. studied | Mean & S.E. | ng/ml Range of prolactin |
|---|---|---|---|---|
| Menstrual cycle | Follicular Phase | 10 | 21 ± 4 | 5 — 30 |
| | Luteal phase | 8 | 43 ± 5 | 18 — 60 |
| | Menopausal and postmenopausal | 12 | 20 ± 3 | 8 — 35 |
| Pregnancy | 1st Trimester | 6 | 30 ± 4 | 15 — 40 |
| | 2nd Trimester | 6 | 111 ± 42 | 24 — 300 |
| | 3rd Trimester | 6 | 270 ± 62 | 80 — 450 |
| Normal men | | 8 | 14 ± 4 | 2 — 41 |

Hyperprolactinemia may or may not be associated with galactorhea. On the other hand galactorhea may occur in the presence of normal serum prolactin levels (Fig. 1).

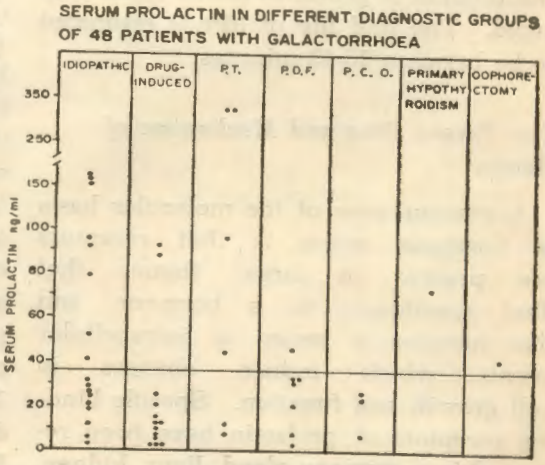


Fig. 1

*Mammogenesis and Lactation*

As the name suggests, prolactin has the main function of preparing breasts during pregnancy (mammogenesis), initiation of lactation (colostrogenesis) and maintainance of lactation (galactopoesis) during postpartum period. Prolactin seems to be increasingly released during human pregnancy and reach peak values near term (Friesen *et al* 1972, L'Hermite and Robyn, 1972). However, for mammogenesis and lactation to be accomplished completely, the supportive actions of other hormones is also required. The mammary stimulation and ductular—lobular—alveolar growth during pregnancy are evoked by luteal and placental sex steroids, placental lactogen, prolactin and probably also by human chorionic gonadotropins. Secretory activity by alveolar mammary cells is evident by midpregnancy, however only small

amount is secreted into the lumen and be expelled from the nipples. Lactation occurring in an individual when pregnancy terminates by 16-20 weeks is not an uncommon clinical encounter. Thus inspite of the possibility of active milk synthesis by midpregnancy only small amount of secretion is released into the lumen during pregnancy. It is only with postpartum withdrawal of placental sex steroids that prolactin is able to fully exert its stimulating effect on mammary target cell for secretory activity. During pregnancy the synthesis and secretion of milk are largely inhibited by prolactin antagonistic effects of estrogen and progesterone at mammary tissue. (Turner 1956, Folley 1956).

Circulating prolactin levels drop sharply after delivery. In non-lactating women they reach to normal non-pregnant levels by 4-6 weeks (Hwang *et al* 1973). In nursing mothers by this time though the levels of prolactin have dropped considerably they remain marginally elevated (Friesen 1972). However, with the stimulus of suckling, prolactin blood levels rise by almost 10 times over basal presuckling values. Since it is known that prolactin levels in milk are higher than serum prolactin levels (Frantz, 1973) and that prolactin in mammary tissue is retained for much longer than in plasma, it is possible therefore, that lactation may be maintained by the periodic rise in prolactin caused by suckling.

*Suppression of Lactation*

Suppression of postpartum lactation may be desired by the patient as she may not want to nurse the baby or it may be required on medical grounds. Suppression may occasionally be required even after an abortion if it is after 16 weeks of pregnancy or following stillbirths.

*Measures and Drugs to Suppress Lactation*

Simple measures like restriction of fluid intake, absence of suckling or manipulation of the breasts, tight and firm support to the breasts may be all that is necessary for cessation of milk secretion. However, very often this may not suffice and drugs may be required to suppress lactation. The success of such simple measures and results with placebo have varied from 13% to 90% in different series (Kantor *et al* 1963; MacDonald and O'Driscoll 1965).

*Drugs for Suppression of Lactation*: Prevention or suppression of lactation can be achieved by following drugs:

1. Estrogens (Watson, 1969, MacDonald and O'Driscoll 1965).
2. Testosterone (Weinstein *et al* 1976).
3. Testosterone and estrogen (Kantor *et al* 1963, Cole and Pitts 1966).
4. Clomiphene citrate (Zuckerman and Carmel, 1973).
5. Bromergocryptine (Rolland and Schellekens, 1973, Weinstein *et al* 1976).

The results of various therapeutic agents have been compared recently in well designed study by Weinstein *et al* (1976). Bromoergocryptine gave 100% results and the best results were obtained when the treatment was started immediately after delivery. Bromoergocryptine, within 3 days of treatment, reduced the high postpartum serum prolactin levels to those found during normal menstrual cycle (del Re *et al* 1973). This much reduction of prolactin is not achieved by the other drugs (Weinstein *et al* 1976). Once prolactin-induced lactation is established it becomes more difficult to suppress it. Long acting androgen estrogen combination also appears to be giving satisfactory results as has been reported by various authors.

*Galactorrhea*: Galactorrhea or inappropriate lactation has been recognised ever since the first description of 2 patients of persistent postpartum galactorrhea by Chiari *et al* in 1855. However, till recently galactorrhea was one of the symptoms and/or signs of cluster of symptoms and sings constituting a particular syndrome named after the physicians who first described and reported them. Thus there have been eponyms for various conditions of galactorrhea which could result from many different etiological factors or different stages of the same etiological factor. These eponyms are important from historical points of view and as documents of keen clinical observation. However, to continue the practice of identifying and describing patients of galactorrhea by these eponyms is confusing and superfluous. The availability of specific assays for prolactin has advanced the understanding of the physiological mechanisms of normal lactation and the pathophysiological mechanisms of inappropriate lactation.

*Role of Prolactin in Galactorrhea*: Abnormal milk secretion in the presence of elevated serum prolactin levels is self-explanatory. It is now well known that patients with hyperprolactinemia need not have galactorrhea. Paradoxically a large number of patients with galactorrhea have normal serum prolactin concentrations. Presence of galactorrhea inspite of normal circulating prolactin level may be due to one or several factors.

(i) The half life of prolactin receptor complex is long and an alteration at night time secretion may be enough to cause galactorrhea where the day time levels could still be normal.

(ii) It is also possible that hyperprolactinemia or the other causative endocrine events that induce galactorrhea may take place prior to the manifestation of galactorrhea. Galactorrhea once established could be maintained by normal prolactin levels.

(iii) Target cell hypersensitivity to normal levels of prolactin.

(iv) Low estrogen levels may fail to antagonise the prolactin action at the target tissue. This may explain galactorrhea in women with premature ovarian failure and in menopausal women.

The underlying mechanism of hyperprolactinemia may be due to (1) a decrease in PIF production or transport, (2) an increase in PRF/TRH or (3) an autonomous functioning of lactotrophs. Etiological factors of hyperprol./galactorrhea are given in Table II.

The incidence of galactorrhea in gynaecological practice depends upon whether the examination of breast for milk discharge is routinely employed in a gynaecological examination or not. A total of 597 patients attending the endocrine clinic for various reasons from Jan. 1975 to Dec. 1976 were screened for galactorrhea. Forty-eight patients (8%) had presence of unilateral or bilateral milk discharge. However, the incidence of galactorrhea in patients with secondary amenorrhea was as high as 18%.

*Evaluation and Management*: Galactorrhea often provides an important clue for an underlying hypothalamo-pituitary disease like pituitary tumor or a systemic disease like primary hypothyroidism (Vaidya *et al* 1977). With this realisation it is important not only to detect the presence of breast discharge but also to have a systematic evaluation of each patient who has galactorrhea. Galactorrhea particularly when associated with

TABLE II

*Etiology of Galactorrhoea*

1. Peripheral Nerve Stimulation

   A. Breast and Chest
      (a) Chest Wall injury or burns
      (b) Post-thoractomy or mastectomy
      (c) Herpes Zoster
      (d) Cystic disease of breast or breast abscess

   B. Uterus and Cervix
      (a) Post-hysterectomy
      (b) Uterine and Adnexal tumors
      (c) I.U.C.D.

2. Inhibition of PIF Synthesis/Transport

   (a) Hypothalamic dysfunction/tumor with decreased production of P.I.F.
   (b) Drug-induced
      (i) Tranquillisers
      (ii) Antihypertensives
      (iii) Hormonal contraceptives
      (iv) I.U.C.D.
   (c) Interference of PIF Transport
      (i) Space occupying lesions
      (ii) Stalk lesions

3. Autonomous Lactotrophic Function

   (i) Prolactinoma
   (ii) Prolactinoma associated ACTH producing tumors (Cushing's disease)
   (iii) Associated with growth hormone producing tumor (Acromegaly)

4. Increased PRF/TRH Activity

   (i) Primary hypothyroidism
   (ii) Hyperthyroidism

5. Removal of Prolactin Antagonising Effect of Mammary Tissue

   (i) Withdrawal of hormonal contraceptives
   (ii) Removal of corpus luteum cyst.
   (iii) Premature menopause
   (iv) Menopause
   (v) Oopherectomy.

amenorrhea demands following investigations:

I Specific History
   (a) Drug intake —
      (i) Hormonal Contraceptives
      (ii) Antihypertensive
      (iii) Tranquilisers
   (b) Headache and giddiness
   (c) Visual disturbances
   (d) History suggestive of hypothyroidism

II Physical examination
   (a) Grading of galactorrhea
   (b) Features of hypo/hyperthyroidism
   (c) Other endocrine stigmata

III Investigations
   (a) Radiological —
      (i) X-ray skull
      (ii) Tomogram of sella turcica
   (b) Ophthalmological —
      (i) Fundus
      (ii) Visual acuity
      (iii) Visual fields
   (c) Hormonal —
      (i) Serum prolactin
      (ii) Serum FSH and LH
      (iii) Serum TSH
      (iv) Serum estradiol

Women with low or normal gonadotropins and elevated prolactin may have (a) pituitary macroadenoma, (b) pituitary microadenoma or (c) diffuse pituitary hyperplasia. 2 $\alpha$-Bromoergocryptine, a dopamine agonist (Parlodel—Sandoz) has been reported to achieve normalization of serum prolactin values and restore fertility, even in cases of pituitary macroadenoma (Aono *et al* 1976). Pituitary adenoma are known to increase in size during pregnancy. This may endanger vision to warrant an emergency treatment of the tumour and/or termination of pregnancy. The tumour should therefore be either removed surgically or

irradiated, before embarking on therapy with Bromoergocryptine.

In the absence of gross enlargement of the sella, elevated serum prolactin indicates a pituitary microadenoma or generalised hyperplasia of the lactotrophs due to a hypothalamo-pituitary dysfunction, (Vaidya *et al* 1978). In the countries where facilities exist for polytomography and transphenoidal microsurgery, the treatment of choice is surgical extirpation. This alone may restore the ovulatory function. The persistence of amenorrhea following microsurgery may be due to the residual hyperprolactinaemia. This is successfully treated with bromoergocryptine. Those patients who have no demonstrable microadenoma should receive bromoergocryptine to correct the reproductive disorder. Bromoergocryptine is available in tablets of 2.5 mg each. Therapy is initiated with a low dose, that is, ½ tablet at bedtime. The gradual increase in dose upto 1.5 mg (2.5 mg three times daily) avoids severe nausea and vomiting. Ovulatory cycles are restored within 6 to 8 weeks of therapy in the majority of cases. Bromoergocryptine should be discontinued as soon as pregnancy is dectected.

*Summary*

The present review deals with the history, chemistry, assay methods, control mechanisms, serum levels, target sites and mechanism of action of human prolactin. The background information provides the understanding to the clinical situations of normal and abnormal lactation and rationale for their appropriate investigations and management.

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