COMPARATIVE STUDY BETWEEN LONG ACTING SINGLE DOSE PARLODEL AND VITAMIN B_6 IN SUPPRESSION OF LACTATION

THESIS

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INTRODUCTION

Mothers should whenever possible breast feed their children. However some circumstances necissetate suppression of lactation such as in late abortion, still birth, immediate postnatal death of the child or in conditions involving the mother health as local disorders of the breast, and systemic disease (severe diabetes mellitus, active pulmonary T.B., decomponsated heart failure, chronic renal failure and intake some urgent drugs such as cytotoxic drugs).

Methods of suppression of lactation have included mechanical compression, fluid restriction, diuretics, synthetic estrogens, androgens, estrogen-androgen combination, Vitamin B_6 (pyridoxine), and more recently Bromocriptine (tablets and single dose long acting I.M. injection).

AIM OF WORK

Comparative study between Parlodel (single dose long acting I.M. injection) and Vitamin B_6 in suppression of lactation in the postpartum period.

EMBRYOLOGICAL DEVELOPMENT OF THE BREAST

At the sixth week of development a thickened ectodermal ridge or milk line appears, which extends along the anterior body wall from the axilla to the groin. The thickening regresses except in the pectoral region, where the mammary gland develops in relation of the second to the sixth rib.

During the fifth month of development a group of fifteen to twenty solid cords grow deeper into the subcutaneous tissue, later on these cords hollow out to form primary milk ducts, which continue to grow and branch, each duct open separately into the body surface in the region that will become elevated to form the nipple. Surrounding the developing nipple the ectoderm becomes pigmented, remains free of hair and develops gland of Montgomery. This areolar region begins to become prior to puberty with subsequent enlargement of the developing breast due to accumulation of fat lobules between developing ducts. At the puberty the ducts continue branching and develop acini at their termination. During pregnancy, the duct and acini become stimulated by steroid hormones to increase in the size and complexity (Langman, 1981).

ANATOMY OF THE BREAST

SITE :

The breast lie within the superficial fascia on the ventral surface of the thorax. They extend vertically from the second rib to the sixth or seventh intercostal cartilage and from the lateral side of the sternum to the midaxillary line. A prolongation of glandular tissue frequently arises from the superiolateral quadrant and extends to the axilla. This mass, the axillary tail of Spence, may pass through an opening in the axillary fascia, the foramen of Longen (Morehead, 1982).

During pregnancy and lactation, breasts increase two or three times in size. Following cessation of lactation, the breasts return to normal size and tend to become more pendulous. The breasts vary considerably in size and shape as compared with general body size. The nipple is usually cylindrical or conical in shape, pigmented and measures approximately 10-12 mm. in height. Minute openings of lactiferous ducts may be retracted beneath the surface of the breast and projects only on stimulation. The mammary gland proper consists of 15-20 lobes with their apices towards the nipple and the bases forming the periphery of the gland. Each lobe has an excretory duct which opens individually on the surface of the nipple. Beneath the areola, the duct increases in the diameter forming the lactiferous sinus. Beyond this dilatation, the duct begins to branch forming lobules and eventually acini.

A single lobe would consist of all the lobules and acini that empty into a single excretory duct. The secretory glandular tissue that forms the parenchyma is surrounded by fatty connective tissue. The dorsal surface of the gland is separated from the pectoralis major and serratus anterior muscles by retromammary fat and loose areolar tissue. Fibrous bands (Cooper's ligaments) interconnect the glandular tissue superficially to the skin and on the deep aspect of the gland, they pass through the retromammary bursa to attach to the fascia of the muscles (Morehead, 1982).

BLOOD SUPPLY OF THE BREAST :

The arterial supply of the breast of the female comes primarily from four sources:

(a) Branches from the internal thoracic artery (internal mammary) which are large and constant.

(b) From the lateral thoracic artery.

(c) Branches from intercostal artery.

(d) Superior thoracic artery.

The arterial pathways enter the gland from the deep surface or from the superiomedial or superiolateral borders. The veins form a subareolar plexus and then join branches from the glandular substance to run to the borders of the gland. In general veins follow the arterial pathways and end in either the axillary vein laterally or internal thoracic vein medially (Morehead, 1982).

NERVE SUPPLY :

The lateral portion of the gland receives sensory innervation from the anterior rami of lateral cutaneous branches from the 4th to the 6th intercostal nerves. The medial portion receives innervation from the medial mammary rami of the anterior cutaneous branches of the second to fifth intercostal nerves. Branches from supraclavicular nerves (cervical plexus) also supply the breast, sympathetic fibers reach the smooth muscles of the areola and nipple, arterioles and glandular tissue by the travelling on adventitia of the arteries (Morehead, 1982).

LYMPHATIC DRAINAGE :

Deep to the nipple and areola a double subareolar lymphatic plexus exists. The deeper plexus drains the superficial plexus and the vessels from the glandular substance. Two major trunks (superior and inferior) pass from this plexus laterally to enter a group of nodes situated along the deep margin of the anterior axillary fold. Subsequent drainage passes through central axillary to apical nodes which in turn communicates with deep cervical nodes in the supraclavicular fossa. Approximately 75% of lymphatic drainage of the breast is directed toward the axilla. The remaining lymphatic drainage passes medially to parasternal channels and nodes associated with the internal thoracic vessels (Morehead, 1982).

PHYSIOLOGY OF LACTATION

Lactation comprises two main phases: first, the milk is secreted and stored within the mammary gland (the phase of milk secretion). Secondly, the stored milk must be made available to the suckling infant as required (the phase of milk removal).

MILK SECRETION :

Milk secretion comprises the process by which the alveolar cells synthesize milk constituents from precursor substances derived from the blood (lactogenesis) and then pass or excrete these constituents into the lumen of the alveolus (Cowie, 1971).

Hormonal Control Of Milk Secretion :

There is no evidence that the activity of the mammary alveolar cells in any way controlled by secretory nerves; indeed the mammary gland can be transplanted to another part of the body and will secrete milk normally as long as satisfactory vascular connections with the general circulation are achieved (Linzell, 1963). The secretory activity of the milk gland is regulated by the endocrine system and in particular by the hormones of the anterior pituitary. The first evidence of the active participation of anterior pituitary hormones in the initiation of milk secretion was obtained by Stricker and Grueter in 1928 (Stricker, 1951). But not till 1971 when human prolactin was isolated by Friesen and his colleagues in Canada and Lewis and his colleagues in U.S.A. (Lewis and Singh, 1973 and Friesen and Hwag, 1974).

In the absence of prolactin lactation does not occur (Tucker, 1979 and Lunn et al., 1980). Increased concentrations of prolactin are of particular importance in the process of lactogenesis whereas only normal non pregnant levels seem to be necessary for the maintenance of lactation once begun (Riddick, 1983). Prolactin through its effect on the alveolar cells activates the synthesis and secretion of milk protein α-lactalbumin, milk fats, and lactose (Archer, 1977). However during pregnancy when the prolactin serum levels are very high up to 200 ng/ml. at term its full lactogenic effect is not yet fully established due to peripheral inhibition created by the also high levels of progesterone and oestrogen (Cowie et al., 1971). When the levels of these hormones drop after delivery milk secretion starts and becomes fully established by the 4^{th}-5^{th} day postpartum (Riddick, 1983). By the 3^{rd} month postpartum the basal non pregnant prolactin levels are resumed, but however, suckling leads to prolactin surges within 15 minutes of nipple stimulation which peaks to levels of 100-200 ng/ml. in the first week, 20-250 ng/ml. during the second to fourth week and from 20-40 ng/ml. thereafter (Riddick, 1983).

Normal levels of cortisol, thyroid hormones, insulin and parathyroid hormone appear to be facilitatory for lactogenesis but only in their normal non pregnant concentrations (Cowie, et al., 1971).

GALACTOPOIESIS :

Galactopoiesis is the maintenance of milk production once it has been established by completion of lactogenesis. The single most important factor in successful galactopoiesis is regular and frequent milk removal from the mammary gland which stimulates further milk secretion by at least three mechanisms (Riddick, 1983). First, regular suckling promotes the regular synthesis and release of both prolactin and oxytocin which are necessary for continued milk secretion. Secondly, the breast has the capacity to store milk for 48 hours before there is a substantial decrease in production due to both decrease prolactin secretion and vascular stasis caused by increased intramammary pressure resulting from distension of the alveolar and mammary ducts with stored milk thus, reducing the blood flow to the mammary gland and consequently reducing the nutrients and hormonal supply necessary for milk production. Thirdly, the amount of milk produced daily is fairly closely related to the demand i.e. to the amount of milk removed the previous day as long as the nutritional and hormonal requirements are met (Riddick, 1983).

MILK REMOVAL :

Milk, when secreted, is stored in the alveoli, ducts, sinuses or cisterns. Only that portion in the large ducts, sinuses or cisterns is immediately available to the suckling. Milk in the alveoli and fine ducts, which may be the greater portion, must be actively transferred into the larger ducts and sinuses before it is available. This transfer is brought about by the contraction of the myoepithelial cells enveloping the alveoli in response to the reflex release of oxytocin into the blood stream usually as a result of the suckling stimulus. This reflex - the milk ejection reflex - is very important for the efficient removal of milk from the mammary gland and failure of the reflex means that little milk can be removed from the gland and repeated failure would lead to the rapid inhibition of milk (Cowie et al ., 1971; Mc Neilly, 1972 and Tindall, 1974). The existence of this reflex has long been recognized and its occurrence in women was referred to as the "draught" (Folley, 1969).

During the last decade the development of sensitive bioassay for oxytocin has permitted the concentration of oxytocin in the blood to be measured during suckling and milking in women (Bisset, 1974 and Tindall, 1974). Milk ejection occurs usually within a minute of the onset of suckling and these then follows as series of rhythmical pressure changes can best be minicked by a series of periodic rapid intravenous injections of oxytocin suggesting that oxytocin release in women during breast feeding occurs in repeated spurts (Caldeyro-Barica, 1969). The intensity of the pressure applied to the nipple by the infant has little apparent influence on the release of oxytocin. A lactile stimulus by itself can usually trigger the reflex although both touch and pressure are normally involved (Luther et al., 1974).

Stimulation of the reproductive tract can bring about the release of oxytocin with the occurrence of milk ejection. Indeed sympathy between the reproductive organs and the mammary gland has long been recognized, from the time of Herodotus agricultural people have used vaginal stimulation to bring about milk ejection in their milk animals thus ensuring efficient milk (Folley, 1969). The occurrence of milk ejection in a lactating woman during coitus and the occurrence of oxytocin in the blood of a woman after orgasm are well established (Fox and Knagg', 1969).

SUCKLING STIMULUS :

The suckling stimulus regulates mammary function in two main ways: first by ensuring the secretion of prolactin and ACTH from the anterior pituitary and secondly by releasing oxytocin from the posterior pituitary.

The sensory innervation of the breast is confined mainly to the nipple (Cowie et al., 1971).

The afferent pathway for both prolactin and oxytocin release is common. Suckling stimulates sensory receptors in the nipple that activate nerve impulses; these impulses are transmitted through thoracic nerves 4, 5 and 6 to the spinothalamic tracts in the spinal cord, terminating in neurons in the mesencephalon. At that point, the pathway divides and the impulses that control oxytocin release travel to the supraoptic and paraventricular nuclei of the hypothalamus where they stimulate both synthesis and release of oxytocin. Oxytocin is released from neurovesicles (Hering bodies) within the neuronal terminals of the posterior pituitary gland. These neurovesicles are located close to the dense vasculature that drains this area. Via B-receptors oxytocin causes the myo-epithelial cells to contract, which results in the release of milk into the lactiferous ducts and sinuses so that it can be removed by suckling. The release of oxytocin becomes a conditioned response in the lactating woman, requiring only visual stimulation or conscious thought. No such conditioned release of prolactin has been demonstrated (Riddick, 1983).

The prolactin pathway continues forward to spreadout in the preoptic area and passes to the medial anterior hypothalamic area close to the third ventricle. A descending prolactin release pathway has also been traced from the orbit-frontal cortex to the preoptic area (Tindall, 1974) and its presence suggests that cerebral cortical control may regulate prolactin secretion and so carries the speculative implication that in man the psychatic state may influence lactation. It is likely that both the ascending and descending prolactin release pathways enter the final prolactin-control mechanism at the preoptic hypothalmic level from which both PIF and PRF are secreted and conveyed to the anterior pituitary in the hypophyseal portal system.

Suckling appears also to activate the release of adrenocorticotrophic hormone (ACTH) simultaneously with the release of prolactin (Meites et al., 1969). The resulting release of