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Role of hormones in persistency of lactation: A review

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Abstract
During lactation, milk production starts increasing until the animal reaches peak yield and thereafter starts declining. So, a better production can be achieved if the animal has lactation persistency i.e. the ability to produce milk at a relatively constant level throughout the lactation. It actually depends upon the mammary cell population and their secretory activity. If these are maintained properly, the animal can continue production for a longer period. Several factors especially hormones affect the proliferation and death of these cells and also their secretory activity. Hormones like growth hormone, insulin-like growth factor-I, thyroid hormones, cortisol, prolactin, insulin, progesterone, estrogen and oxytocin play a major role. So, the objective of this review is to discuss the role of the hormones in lactation persistency so that it can be improved and higher production can be obtained.

Keywords: Lactation persistency, milk, hormones, BST, IGF

1. Introduction
Milk is one of the most nutritious food item consumed by the people on a regular basis. In India, the major sources of milk come from domestic species like cattle, buffaloes etc. Milk is obtained from the animals after parturition throughout its lactation period. In the case of cattle, the maximum milk yield is observed at 4-6 weeks after parturition then afterward it starts declining. Indeed, the level of peak yield and the rate of decline in production after peak yield with the progression of lactation determine the shape of the lactation curve. So when the animal is maintaining a constant milk yield throughout their lactation that is lactation persistency; reflects a more milk production by the animal. Persistency can be defined as the potential of the animal to the continuous production of milk at a relatively high rate after peak lactation. Better persistency will lead to better production and a better economy. The welfare of the animal is also maintained in longer lactation because the animal is less exposed to the parturition and lactation stress [1]. So it is important to know the physiological mechanisms behind the persistency of lactation; which are predominated by different hormones. GH, IGF-I, Thyroid hormones, Cortisol, Prolactin, Insulin, Progesterone, Estrogen and Oxytocin are the main hormones which regulate development of mammary gland and production and secretion of milk [2]. The role of these hormones and their mechanisms are described below.

2. Calculation of Lactation persistency
There are several methods of estimation of persistency. These can be broadly classified into three categories: 1) Ratio method 2) Variation of yields method 3) Mathematical lactation curve model [3]. Examples of ratio methods are Rao and Sundaresan method [4] and $TOMAX_2$ and $TOMAX_3$ measure [5]. Solkner and Fuchs methods [5] and Gengler and co-worker method [6] are different types of Variation of yields method. Wood's gamma function [7] is one of the examples of Mathematical lactation curve model. Among these, the estimates of persistency derived from ratio method is considered to be most effective as compared to other methods [3]. The formula for estimation of persistency (P) through Rao and Sundaresan method is given below.

$$P = \frac{\text{Lactation Milk Yield}}{\text{Peak Yield}}$$

3. Role of mammary epithelial cells in the maintenance of persistency

Different types of cells are found in the mammary glands, like epithelial, adipose, fibroblast, immune, lymphatic and vascular cell [8]. Collaborative works of these cells make a mammary gland functional. As the animal undergoes different stages like pregnancy, lactation and involution; the cells of the mammary gland also go through proliferation, differentiation and apoptosis [8]. Among these mammary epithelial cells and their secretory activity determine ultimate production in a lactating animal. With species differences, increased number and activity of mammary secretory cells results in increased milk yield to peak lactation and vice versa [9]. In bovines, Capuco and co-workers observed the changes in mammary cell numbers and secretory activity during lactation in non-pregnant multiparous cow [10]. Before peak lactation, there was only increased secretory activity with a constant cell number. But after peak yield, there was a decreased cell number with a non-significant change in secretory activity (Table.1). In case of a pregnant lactating cow, the secretory activity also decreased with the advancement of pregnancy due to the conflict of metabolic demands of lactation and gestation. At the time of late pregnancy though the number of epithelial cells increased there was a decline in milk production concurrently [11]. In goats, Knight and Peaker did a similar study [12]. And their results revealed that unlike bovines both increased mammary cell numbers followed by increased activity resulted in increased milk production. Afterward, the decrease in cell numbers caused decreased milk yield with the advancement of lactation (Table.1).

Table 1: Events during early and late lactation of bovine and caprine

	Bovine		Caprine	
Phases	**Early lactation**	**Late lactation**	**Early lactation**	**Late lactation**
Cell number	Constant	Decreased	Increased	Decrease
Secretory activity	Increased	Non-significant change	Increased	Non-significant change
Milk yield	High	Low	High	Low

It is evident from the above discussion that, there is a loss of cells through apoptosis after peak lactation in both the species. Therefore, better persistency and milk yield can be obtained through maintenance of mammary epithelial cells population. From different experiments it has been proved that; nutritional, lactational and reproductive managemental techniques can be helpful in the survival of the cells.

4. Role of hormones in persistency

Besides hormones, several other factors which affect the persistency of lactation are metalloproteinase activation, dietary factors, alveolar distension, FIL (Feedback Inhibitor of Lactation) and IGFBP-5 (Insulin like Growth Factor Binding Protein-5) [13]. But the hormones like GH, Cortisol, IGF, T_3, T_4, insulin, estrogen, progesterone and oxytocin play the most important role in combination with other factors for maintenance of persistency.

4.1 Bovine growth hormone

Bovine somatotropin or bovine somatotrophin (bST or BST) or bovine growth hormone (BGH), is a peptide hormone produced by cows' pituitary glands. Importantly its effect is mediated by insulin like growth factor-I (IGF-I) [14]. As stated earlier, the decline in milk yield with the advancement of lactation is mainly due to decreased cell number not in cellular activity. The effect of bST on persistency is due to maintenance of cell population rather than secretory activity. Its role in the maintenance and proliferation of cells in late lactation has been established in bovine, caprine and ovine also [9, 15–17]. Exogenous administration of GH in cattle and buffaloes has also shown to increase milk yield [9, 18].

In the year 1979, rBST (recombinant bovine somatotropin) was made in bioreactors (an *Escherichia coli* strain) [19]. Like GH, exogenous injection of rBST has both mammary local effects and metabolic effects along with the increase of insulin-like growth factor 1 (IGF-1) protein in liver and mammary tissues [20]. Local effects are to increase IGF-1 expression in mammary tissue, MEC (Mammary Epithelial Cell) proliferation and survival and milk synthesis rate by MEC. Metabolic effects are to increase basal metabolic rate, blood flow, lipolysis, gluconeogenesis, IGF-1 blood level and 1, 25 dihydroxycholecalciferol. All these effects combine together and help in the maintenance of mammary epithelial cell population as well as constant milk production by the animal.

GH also plays interactive roles with Prolactin. A decrease in GH level can result in a 15% decline in milk yield, prolactin a 50% decline and combined prolactin and GH deficiency an 85% decline in milk yield. GH- and prolactin-deficiency also led to significant loss of mammary cells within 48 h [21].

4.2 Insulin like growth factor

IGF is primarily produced from liver upon stimulation of GH (Fig.1). IGF has anti-apoptotic action on different cell types and hence used in the treatment of several tumors and prevention of apoptosis. It affects mammary development by acting on both the progression of cell cycle and cell death [22]. It can induce cell proliferation *in vitro* as well as *in vivo* mammary model systems [22, 23]. If the expression of IGF is prolonged in the mammary gland, the lactation is also prolonged with the delay in involution [24].

The activities of the IGFs are controlled by a family of proteins called the insulin-like growth factor binding proteins (IGFBPs). IGFBPs generally act as a carrier protein for IGF, but sometimes block their activities within the tissue by binding with them (Fig.1). There are several members in the IGFBP family with species differences. In bovines, four types of IGFBPs (-2, -3, -4 and -5) are expressed [23]. Among them, IGFBP-3 is expressed in the mammary gland of ruminants in the early stage of involution. Through binding with IGF, it inhibits cell survival and initiates apoptosis which is an important event of mammary involution. With this dramatic increase in level during involution it acts as a 'cell suicide' factor [24]. Reversibly, the level is declined during lactation. If there is over-expression of IGFBP-3 in mammary tissue of the lactating animal, there will be a decrease in mammary epithelial tissue resulting in decreased milk production [24]. In the case of rat, mouse and pig these functions are done by IGFBP-5.

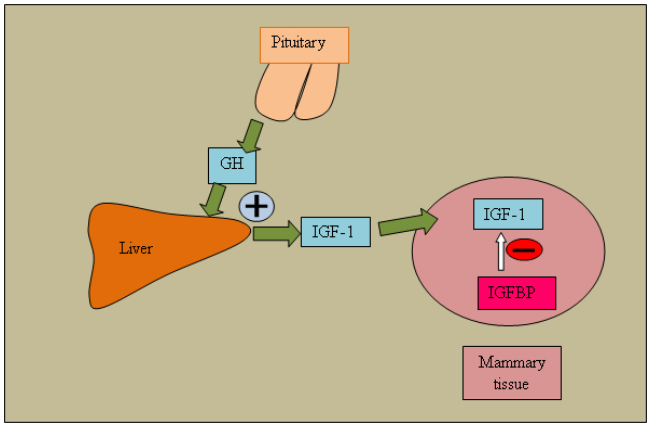

Fig 1: Interaction of GH, IGF and IGFBP. GH stimulates liver for secretion of IGF. IGF acts on mammary tissue, where it is inhibited by IGFBP. [(+) indicates stimulation and (-) inhibition].

4.3 Prolactin

Prolactin has a direct effect on prolonging of lactation or lactation persistency. It acts together with GH as a stimulator of IGF-1 and potent inhibitor of IGFBP-5 expression resulting anti-apoptotic effect [24]. So after weaning when prolactin level is decreased, apoptosis is stimulated by the appearance of IGFBP [1]. It has been observed that persistency is increased when the frequent milking is practiced along with treatment of GH [15, 25]. Actually, frequent milking causes in up-regulation of the prolactin receptor, as a result, all the factors necessary for persistency are brought together [26].

4.4 Cortisol

In ruminants, the effects of high doses of glucocorticoid are inhibitory, but the effects of lower doses are ambiguous. In case of rats, at lower doses (more physiological) exogenous glucocorticoid stimulates milk yield in early lactation. If adrenalectomization is performed in rats, milk secretion is impaired but cortisol administration can reverse this [27]. Cortisol acts during puberty, pregnancy and lactation in coordination with other hormones and helps in the development of mammary gland and also in the secretion of milk. The role of cortisol in mammary development at different stages of life is depicted below (Fig.2).

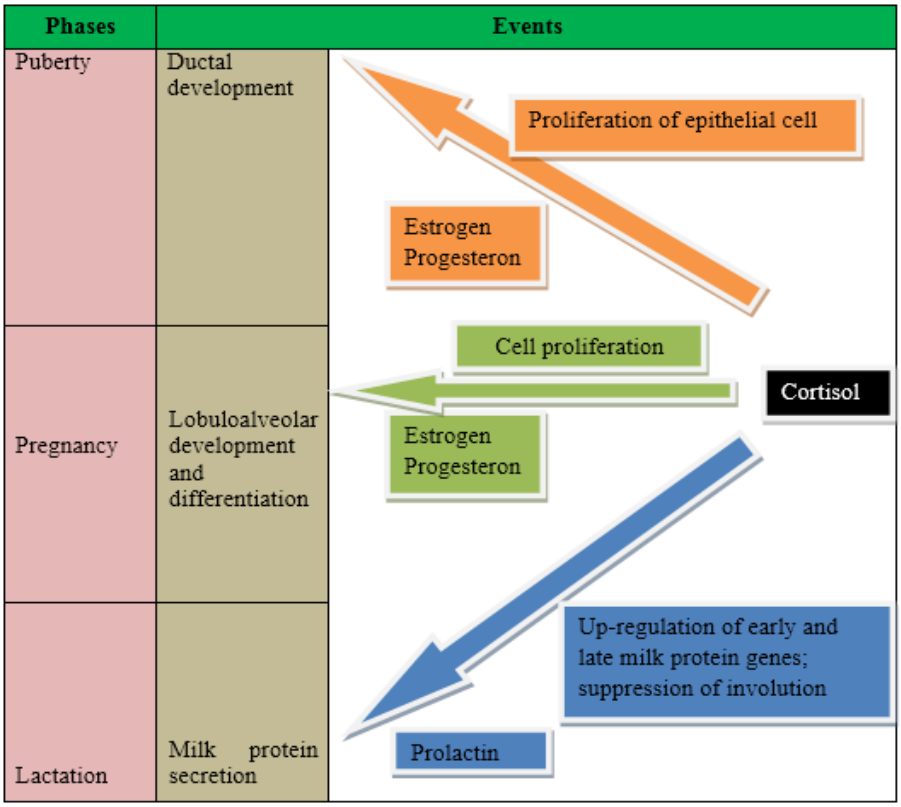

Fig 2: Role of cortisol in mammary gland development [28]

4.5 Thyroid hormones

Thyroid hormones generally regulate different metabolic processes in the body. In the mammary gland, it helps in the differentiation of the epithelial cells [29]. Different in-vivo and in-vitro studies have proved that exogenous injection of thyroid hormone can increase milk production potentiating other lactogenic and galactopoietic hormones [30, 31]. Feeding thyroprotein (iodinated casein) to cows also increases milk yield by 10 % in early lactation and by 15-20% in late lactation [32]. Conversely, thyroidectomy in cattle results in decreased milk yield. The secretions of thyroid hormones are stimulated by thyroid releasing hormone (TRH). This TRH also triggers the fast release of prolactin [33]. Thus it potentiates the anti-apoptotic mechanisms through the help of prolactin.

4.6 Insulin

Insulin can stimulate cell division for different types of cells in the cultured condition [34]. Mammary epithelial cells are also not an exception [35]. However, this effect of insulin is pronounced not in physiological concentration but in pharmacological concentration. It has been reported that pharmacological concentration (>175 pmol/ml) of insulin and a physiological concentration (39 pmol/ml) of recombinant human insulin-like growth factor-I (rhIGF-I) stimulated DNA synthesis in bovine mammary tissue in-vitro [36]. Though, no

synergistic effect was found between them. It also helps in growth and modulation of myoepithelial differentiation [37]. It is said that insulin has acquired its mitogenic activity due to structural similarity with IGF-1, a potent mitogen. This results in the binding of insulin with IGF receptors and performs its function [38].

4.7 Estrogen
Estrogen is one of the major hormones for mammary gland development. It stimulates the action of GH for the synthesis of IGF mRNA. It also enhances the effect of IGF on mammary gland [38]. On the other hand, exogenous administration of estrogen can inhibit lactation as it interferes with milk-ejection reflex [39].

4.8 Progesterone
Exogenous administration of 17β-estradiol and progesterone for 7 days can initiate lactation in non-lactating bovines [40] though its administration does not affect milk yield in lactating cow.

4.9 Oxytocin
Oxytocin acts at the mammary glands, causing milk to letdown as a result of suckling reflex [41]. In the case of the rabbit, it also induces exocytosis of milk synthesis in the mammary epithelial cells (MEC) [42]. By acting on myoepithelial cells, it induces milk ejection and this milk removal also helps in removal of feedback inhibitor of lactation (FIL), a milk glycoprotein that induces reversible block of protein synthesis of the MEC. Thus, reduction of FIL induces milk synthesis [43]. It also helps in the maintenance of the integrity of mammary epithelial cells.

5. Heat stress and lactation
Heat stress is a matter of major concern as it adversely affects both the quality and quantity of milk production [44] and impacts persistency. It causes these changes through altered endocrinological balance and pathological changes. Cows producing more milk are more affected as they are already in lactational stress. It results in an increase in body temperature, respiration rate and impaired feed intake. All these effects alter the hormonal profile of the animal. Hormones like prolactin, thyroid hormones, glucocorticoid, GH, adrenocorticotropic hormone (ACTH), oxytocin, estrogen and progesterone are changed [45, 46]. It has been observed that the level of PRL, Oxytocin, TSH, Estrogen, T_3 and T_4 are decreased whereas the level of ACTH, Glucocorticoid, GH and Progesterone are increased as depicted in the diagram below (Fig.3). In addition, heat stress also enhances mammary involution through increasing apoptosis and decreasing epithelial cell number [47]. So, if persistency is to be maintained, the heat stress should be removed from the animal through different managemental practices.

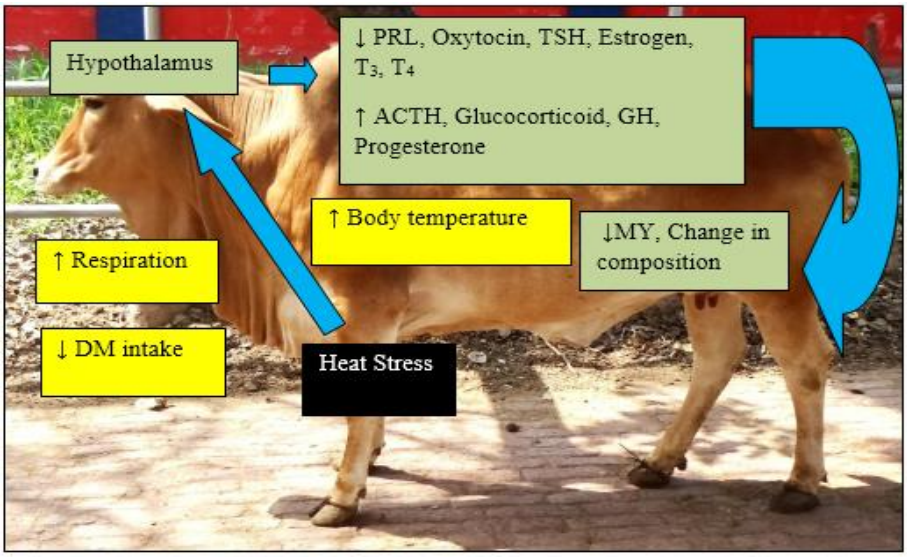

Fig 3: Pictorial representation of heat stress impacting milk production in dairy cattle through alteration of endocrinological balance (PRL- Prolactin, TSH- Thyroid stimulating hormone, T_3- triiodothyronine, T_4- thyroxine, MY- Milk yield, DM- Dry matter, ↑- Increased, ↓- Decreased) [47]

6. Managemental practices for improving persistency
It has been discussed earlier that the administration of hormones (e.g. bST) can improve persistency, but more profitable and long-lasting effects can be achieved through proper managemental practices [48]. Reproductive management is one of the appropriate ways to extend lactation period [49]. Factors like feeding level or milking frequency also have a clear impact on mammary cell apoptosis and tissue remodeling, which control the rate of decrease of milk yield after the lactation peak [9].

6.1 Breeding Management
After achieving a peak yield, milk production starts declining. So, to get next lactation yield the animal is bred subsequently. As a result, when the animal is in lactation, it is pregnant too. Again this pregnancy impacts on production due to metabolic conflict. So, our strategy should be extended lactation, when the breeding is delayed and persistency is maintained through managemental practices [49]. The welfare of the animal is also maintained when the lifetime health is considered. It has been observed that 65% of the health problems happen in 0-45 days of lactation [50]. So, less number of calves a cow produces, less exposed to stress it is. Suppose a cow calves three times with 12 months lactation cycle, in extended lactation, it will calf for two times if lactation is of 18 months. By this way, one-third of the health problems can be reduced [49]. The ovarian problems are also less and the conception rate is more in case of longer calving interval [50]. Regarding the economic

point of view, studies have shown that high producing cows give more yields in longer lactation period compared to 12 months lactation [51]. Though, in that condition, the dry period was also lengthened making it economically non-practical, because no effort was made to maintain the lactational persistency. Extended lactation will be successful only when persistency will also be maintained simultaneously. So, it is clear that extended lactation will benefit both animal and farmer. The extended lactation with persistency can be achieved through optimizing nutrition and milking frequency.

6.2 Nutrition

Nutrition has a pronounced effect on each and every physiological function. Mammary gland development is also not an exception to it [13]. Studies have shown that, if heifers are fed high energy diet feed (75% concentrate) for first eight weeks of lactation, the proliferation of mammary epithelial cells are increased eleven times compared to low energy diet (25% concentrate) fed animals [52]. Though, the rate of cell death was not affected significantly in this case. At the declining phase of lactation also, the persistency can be improved through appropriate dieting programme [53]. On the other hand, apoptosis can be increased due to oxidative stress. It is the result of the excess generation of reactive oxygen species or reduction in activity of antioxidants of the mammary epithelial cells [54]. In this condition, dietary antioxidants can be provided with feed to control oxidative stress [55]. So, proper selection of the nutritional programme should be done to minimize oxidative stress and increase cell proliferation.

6.3 Milking frequency

It has been reported that milking frequency modulates both milk yield and lactation persistency in mid-lactation cows. Milking frequency actually affect the response of mammary gland to hormones like prolactin and IGF-I [56]. Undoubtedly increasing milking frequency from two to three or four times a day increases milk yields [57]. However, economics and especially labor costs and availability of labor are also major factors to be considered. It was observed that glands of lactating goats milked three times daily contained more luminal epithelial cells than the contralateral glands in the same animals milked twice daily [54]. So, it is obvious that the management of milking frequency has the potential to be beneficial not only during early lactation but also later in lactation [58] and can help in improving persistency of lactation.

7. Conclusions

Maintaining lactation persistency is important to get a higher milk production from the animal. Besides increasing the farmers' income it also secures animal welfare. We have also discussed that maintaining the mammary cell population and their secretory activity for a longer period is the key for a good persistency. So our target should be increasing the mammary glands' ability to replace those cells that die during lactation. Several hormones play a vital role in proliferation, differentiation and survival of these cells. Though exogenous administration of these hormones can improve persistency; a long-lasting effect can only be obtained through good managemental practices. Breeding management along with proper nutrition and increased milking frequencies can help in achieving lactation persistency as well as higher milk yield for an extended period.

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