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Factors regulating ovine reproduction: A mini review

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Abstract
Sheep production systems are mainly subsistence-oriented but in view of the rising demand for meat, there is a great scope for their commercialization. The major reasons for low productivity are inadequate grazing resources, high mortality, morbidity due to different disease condition, poor hygienic condition and consequently reduced production, and serious lack of organized effort for bringing genetic improvement. The reproductive efficiency of different breeds of sheep in India is relatively low Induction of cyclicity in out of breeding season and controlling the estrus cycle during the breeding season in an effective and economical way is a very challenging task for the producers to increase overall profit. Various factors affecting sheep reproduction are briefed in this manuscript.

Keywords: Sheep, seasonality, photoperiod, reproductive efficiency

1. Introduction

Livestock sector plays a crucial role in rural economy and livelihood in India. Livestock is an integral component of agriculture in India and make multifaceted contributions to the growth and development of the agricultural sector as well as the overall economy. Livestock contributes significantly in food stream, nutrition, income, asset savings, soil productivity, livelihoods, transport, agricultural traction, agricultural diversification and sustainable agricultural production, family and community employment, social status and also performs few other functions [3]. Sheep constitute a very important species of livestock in India, mainly due to their short generation intervals, higher prolificacy rates and the ease with which their products *viz,* meat, wool and milk can be marketed. The increasing global demand for livestock products is an opportunity for India to increase its exports. Meat exported from India is risk-free, lean, nutritious and competitive priced meat. India is the largest exporter of sheep meat in the world. The country has exported total (sheep and goat) 22,060.15 metric tonnes meat to the world for the worth of` 871.08 crores/ 130.17 Million USD during the year 2016-17. Total Sheep Population in the country is 74.26 Million during the year 2019 and has increased by 14.13% over the 19thlivestock census [1]. Sheep husbandry is a source of livelihood and economic sustenance among poor farmers of dry plain, mountain, and hilly regions of the country. The frequent drought and famine situations and continuous decline of grazing resources both in terms of quality and quantity could be the reasons for the decline of sheep in certain states. India's sheep husbandry depends largely on the monsoon and changing rainfall patterns in western and central India would cause scarcity of grazing resources. India possesses the largest livestock population in the world and accounts a third-highest number of sheep (5.7%) in the world. India is host to 65 million heads of sheep with a slaughter rate of 32% and an average carcass weight of 10 kg and contributes 208 million kg meat, 28 million pieces of skin and 47 million kg wool to GDP [17]. The relatively lower slaughter rate and population growth of Indian sheep are primarily due to relatively lower reproductive efficiency (65–70%) in farmers' fields. The sheep, in relation to other livestock species, is well adapted to different climatic conditions and its vagaries.

The future growth in the livestock sector needs to be focused on productivity and efficiency. The sector is also being considered to play a promising role in the ambitious goal of the government to double the farmer's income by 2022 [5, 8]. The livestock sector in India has strong backward and forward linkages and promotes many industries like livestock-based food processing and leather industries [18]. Livestock is one of the fastest-growing agricultural sub-sectors in developing countries and indispensable to the economic, nutritional, and social well-being of the farmers. Sheep play an important role in the Indian economy by providing employment to a large population of marginal and landless farmers. The production from native breeds is relatively low due to their poor reproductive efficiency.

2. Reproductive cycle of sheep

Reproduction in sheep follows a seasonal pattern by alternating periods of anoestrus and periods of sexual activity. Breeding season start when day length become short as in winter that why ewes called short-day breeder. Sheep is a seasonally polyestrous animal and normal ovulatory cycles occurs in winter. There are typically 3 or 4 waves of follicle development during the inter-ovulatory interval. A wave-like pattern of antral follicle development in sheep is manifested as a synchronized growth of 1-4 small (i.e., 2–3 mm) follicles to ostensibly ovulatory sizes, in both ovaries, following a rise in mean serum concentrations of FSH. The wave pattern is initiated prior to the attainment of puberty in ewe lambs and in sexually mature ewes is interrupted only during gestation and the early post-partum period [3]. Patterns of reproductive activity in the adult, non-pregnant ewe are dominated by two distinct rhythms, first of these is a 16- to 17-day long estrus cycle and the other is an annual rhythm of ovarian cyclicity characterized by a season-dependent cessation (anestrus) and restoration (breeding season) of ovulatory ovarian cycles [23]. The growth of ovarian follicles attaining ostensibly ovulatory diameters exhibits a distinct wave-like pattern at all stages of the breeding season and throughout seasonal anestrus in ewes [26]. On the basis of the ovarian structures the estrus cycle has been divided into a follicular phase of duration 3-4 days and the luteal phase of average 14-15 days, luteal phase is characterized by the maturation of the corpus luteum and high levels of progesterone that reach a maximum peak about 6 days after ovulation [16]. Antral follicular development is closely associated with periodic elevations in daily serum concentrations of follicle-stimulating hormone (FSH) peaks of transient increases in daily FSH concentrations occur just prior to follicle wave emergence. Corpus luteum (CL) of the ewe's estrus cycle is formed mainly by the action of luteinizing hormone (LH), involving a cascade of functional and phenotypic changes in the granulosa and theca cells of ruptured follicles. The increased estrogen level due to large size follicles leads to behavioural estrus signs like stimulation of cervix to secrete small amount of mucus, increased vascularization in the vulva (edematous vulva) and some changes in the epithelial tissue of the vagina.

Estrus in the ewe is less apparent as compared with other ruminant species. During the proreceptivity period, the ewe will be attracted toward the ram, showing mutual sniffing, frequent micturition and licking followed by receptivity when the ewe stands to be mounted. The duration of the estrus behaviour is about 30 to 48 h depending on the breed. Ewes normally ovulate 24 to 27 hours after the onset of estrus and after ovulation, the entire progesterone is secreted from the corpus luteum formed under the sole effect of LH. The mature size of CL (11-14 mm) is attained around day 6 after the initial luteogenesis and it undergoes atrophy abruptly over 2-3 days at about 12-15 days of ovulation under the effect of PGF2α. It has been observed that during the transition from breeding period to the seasonal anestrus, the failure of initiation of follicular waves occur due to inability of FSH peaks, low level of luteal progesterone and low estradiol production which may be attributed to decreased sensitivity of ovary to gonadotropins. The estrus cycle is associated with a sequence of inter-related endocrinological events regulated by the hypothalamus producing GnRH; the pituitary gland secreting FSH, luteinizing hormone (LH) and oxytocin; ovarian antral follicles secreting estrogens and inhibin; the CL secreting progesterone and oxytocin; and the uterine endometrium producing PGF2α. Progesterone appears to be a key endocrine signal governing the control of periodic increases in serum FSH concentrations and the number of follicular waves in cyclic sheep. Two mechanisms may be responsible for the regulation of the number and periodicity of FSH peaks by progesterone throughout the ewe's estrus cycle. Firstly, the pituitary gonadotrophs are stimulated by GnRH to synthesize and release both LH and FSH from the anterior pituitary gland and with GnRH pulsatility remaining low, FSH secretion is favoured over LH. Secondly, circulating progesterone concentrations may dictate the clearance rate of circulating FSH. During the transition from the breeding season to anestrus in ewes, follicle wave emergence is transiently dissociated from FSH secretion as some FSH peaks fail to initiate the emergence of a follicle wave.

2.1 Seasonal breeding in sheep

Sheep are widely known as an animal with marked seasonality of breeding activity. The annual cycle of daily photoperiod has been identified as the determinant factor of this phenomenon, while the environmental temperature, nutritional status, social interactions, lambing date and lactation period are considered to modulate it. Another mechanism is a reproductive strategy involving a 'natural contraceptive method' which restricts the reproductive activity to the best time of the year for assuring that births occur at a time suitable for maximal growth and development of the offsprings and lactation in the mother, however, it is undesirable from an animal production point of view [7] In cold and temperate regions, this period corresponds to spring or early summer while in hot arid climates it coincides with the rainy season. The seasonality in breeding is much pronounced in the temperate climates as compared to tropical and sub-tropical. In the tropical zones, sheep tends to breed throughout the year as there is less variation in day length; therefore, when temperate breeds are introduced into the tropics, they gradually lose their seasonality and follow the breeding patterns characteristic of the new environment (24). In general, the higher the latitude the greater the photo dependence and the more restricted the period of breeding activity. The breeding season starts in most ovine breeds during summer or early autumn and its length varies largely among breeds but in general it ends during the winter. Reproductive seasonality in the ewe is characterized by changes at behavioural, endocrine and ovulatory levels, in an absolute fashion giving rise to an annual alternation between two distinct periods; a breeding season, characterised by the succession at regular intervals (mean of 17 days) of estrus behavior and ovulation, if a pregnancy does not develop, and an anestrous season characterised by the cessation of sexual activity follows. Silent ovulations, not related either to the onset or the end of the sexual season, may also occur in some breeds during mid-anestrus.

2.2 Role of photoperiod in seasonal breeding

Day length or photoperiod is a key regulator of reproduction in seasonal breeder mammals. Photoperiod along with different factors seems to be responsible for seasonal behaviour in animal reproduction. Day length has a dominant controlling influence on initiation and termination of the breeding season in temperate regions. As the ratio of daylight to darkness decreases the breeding season of sheep is initiated and increasing day length i.e. equal daylight and darkness lead to end of the breeding season. The short-day length during the winter season have a stimulatory effect on the reproductive neuroendocrine axis in sheep which leads to ovulatory cycles and fertility resumption while the long day length has an inhibitory effect on hypothalamus-pituitary-gonadal axis leading to anestrus [14]. So, ewes are classified as short-day breeders in contrast to long day breeder such as the mare. Artificial reversal of the annual rhythm of photoperiodic variations induces reversal of the period of ovulatory and estrus activity in the ewes. Finally, the alternation of 3 or 4 months period of constantly long (16 h of light–8 h of dark) and constantly short (8 h of light–16 h of dark) days induces the alternation of periods of sexual activity and inactivity in the ewes. The levels of circulatory progesterone remain low and no gonadotrophins surges are observed during the seasonal anestrus. The study of follicular dynamics by ultrasonography has shown the existence of waves of follicular development in the seasonal anestrous. The pineal gland functions as a transducer converting neural information regarding the light-dark cycle into a hormonal signal which takes the form of a circadian rhythm of melatonin secretion. The pattern of this melatonin signal, which can be interpreted as inductive or suppressive, sets the frequency of the LH pulse generating system and determines its capacity to respond to the negative feedback action of estradiol. It has been evidenced that the eye of the mammals is the only photoreceptor organ responsible for the photoperiodism [31] and the retina of mammals transmits the photoperiodic information to suprachiasmatic nuclei (SCN) of the hypothalamus which exerts its control over pineal gland for nocturnal production of melatonin (22). SCN seems to be the master circadian pacemaker located in the hypothalamic region of the brain in mammals (31), while photoperiod is the main determinant of seasonality.

2.3 Melatonin a regulator of seasonal breeding

Melatonin is a neuroendocrine hormone secreted by the pineal gland. Its secretion is regulated by light and dark stimuli, and the hormone influences circadian rhythms, such as the sleep cycle and body temperature. Melatonin may play a role in pubertal development and the reproductive function by regulating the hypothalamus–pituitary–gonadal axis. Melatonin (N-acetyl-5-methoxytryptamine), the hormone of the pineal gland, exhibits a circadian rhythm that is generated by the circadian pacemaker situated in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is synchronized to 24 h, primarily by the light–dark cycle acting via the SCN. Melatonin receptors subtypes MT1 and MT2 are expressed by different body tissues but pars tuberal is (PT) region of the anterior pituitary express the maximum MT1 subtype, with its pivotal role in seasonality by control over the production of gonadotropins (LH and FSH) and prolactin [2, 30]. Melatonin receptors have been identified in hypothalamic neurons governing the release of pituitary gonadotropins and in the gonadotrophs of the anterior pituitary. Melatonin hormone follows a circadian rhythm with significant secretion occurring only during the dark period of the day with the light acting as a suppressor. Consequently, melatonin levels in both the pineal gland and the blood are high at night and low during the day. The question of which parameter of the nightly melatonin secretion is used to measure the day length (i.e. amplitude, duration or phase relative to the 24 h light/dark period).It is known that this effect of melatonin involves modulation of the secretion of gonadotropin-releasing hormone which leads to the induction of estrus cycle in the sheep. Melatonin also governs the control over the production of thyrotropin hormone (TSH) from the pituitary which is secreted in high quantity during long summer days [31, 7]. From the two major hypotheses that have emerged, the "phase hypothesis" and the "duration hypothesis", it seems that the most convincing evidence to date supports the "duration hypothesis" because sheep have been shown to respond to the melatonin signal irrespective of when it is received during the 24 hr period. ROS produced within the follicles, especially during the ovulation process, are scavenged by melatonin, while reduced oxidative stress may be involved in oocyte maturation, embryo development and luteinization of granulosa cells.

2.4 Role of thyroid hormones in seasonal breeding

Thyroid gland removal stops the development of photo-refractoriness (i.e., insensitivity to previous stimulatory day-length) and if carried out during the refractory period leads to its spontaneous dissipation. Thyroid hormones are required for the transition from breeding to anestrus state but not for the reverse transition from anestrus to breeding season. In short-day breeders, the longer photoperiod induces the expression of DIO2 (Deiodinase 2) which converts T4 into T3 leading to termination of breeding season (13) and also T4 administration terminates breeding season *via* decreasing serum LH. Sheep usually breed during the autumn/winter season of the year when day length is short [15] and displays TSH-DIO2 response whereby leading to increased production of tri-iodothyronine (T3) during the long summer days with impaired breeding activity [14]. It has been proposed that T3 acts via the nuclear receptors in the medio-basal hypothalamus (MBH) and other areas of brain [19] and Kiss1 and Rfrp genes which encode the neuropeptides KISS1 and RFRP3 (RF-amide–related peptide-3) seem to be major targets of thyroid hormones in MBH with context to seasonal breeding [7]. In sheep, thyroidectomy stops the development of refractoriness in ewes and rams.

Thyroid hormones are probably involved in the alterations in the responsiveness of the GnRH axis to the negative feedback effects of estrogen during the transition to anestrus. Thyroid hormones are required for steroid-independent cycles in LH pulse frequency; however, some seasonal changes in amplitude still occur in the absence of thyroid hormones. This finding contrasts with the changes in estradiol negative feedback at the transition to anestrus, which are entirely thyroid hormone-dependent. The primary neuroendocrine mechanism underlying the occurrence of seasonal anestrus involves a marked increase in the responsiveness of the hypothalamic GnRH pulse generating system to estradiol negative feedback. In the absence of estradiol, a seasonal decline in LH pulse frequency and an increase in pulse amplitude occurs gradually beginning in late winter, approximately concurrent with the lengthening of photoperiod.

2.5 Neural mechanisms as a regulator of seasonal breeding

The neural circuitry within the hypothalamus of female sheep responsible for E_2-negative feedback during anestrus. Seasonal reproductive transitions in the female sheep are a direct result of striking changes in the ability of E_2 to inhibit GnRH; specifically, during anestrus, E_2 gains the ability to dramatically suppress the frequency of GnRH and LH pulses. The impaired GnRH activity prevents the rise in LH which is necessary for the late follicular phase peak in estradiol which induces GnRH/LH pulses for ovulation [11]. Because of this increased responsiveness to E_2 inhibition, even the low levels of E_2 present during anestrus strongly inhibit GnRH activity, preventing the rise in LH necessary for the late follicular-phase peak in E_2 th]. Even though ovulation is blocked during anestrus due to increased E_2 negative feedback, the surge mechanism is still intact, and exogenous E_2 can induce a positive feedback response and produce a GnRH/LH surge. Thus E_2 negative, but not positive, feedback is under seasonal control, and an initial approach to uncovering the neuroendocrine changes responsible for seasonal breeding in sheep has focused on under-standing how this negative feedback influence is conveyed to GnRH neurons. Because GnRH neurons lack the alpha isoform of the estrogen receptor, the isoform responsible for the negative feedback influence of E_2 on GnRH secretion.

Dopaminergic neurons in the retrochiasmatic area (RCh), known as A15 group of neurons also had been displayed to have a role in seasonal breeding in sheep [27, 28]. Dopamine (DA) D2 receptor antagonists, administered either peripherally or intracerebrally, block the ability of E_2 to inhibit GnRH/LH pulses during anestrus in female sheep. This implication of the involvement of DA in seasonal breeding led to the discovery of a key set of dopaminergic neurons within the retro chiasmatic area (RCh), known as the A15 group, that is now believed to play a critical role in seasonal regulation of GnRH secretion [28]. Finally, neural activity studies have shown that E_2 increases tyrosine hydroxylase (TH), the rate-limiting enzyme for DA synthesis. Two primary areas of estrogen-responsive cells that are activated during estradiol negative feedback, specifically during anestrus: the ventromedial preoptic area (vmPOA) and the retrochiasmatic area (RCh) [25] Estradiol also increases the neural activity of tyrosine hydroxylase (TH) which is rate-limiting enzyme in the synthesis of dopamine. D2 dopamine receptors are present in the GnRH neurons of sheep where dopamine directly inhibits the GnRH pulses by acting at the GnRH axons [12].

3. Strategies to combat seasonal breeding and improving reproductive efficiency in sheep

The reproductive efficiency of sheep is a major determining factor in the profits earned by sheep farmers. Reproductive seasonality is one of the constraints in achieving higher reproductive efficiency in ewes. Different strategies like feeding management, photoperiod management, the introduction of the male in the flock and use of different hormones either alone or in combinations for estrus synchronization has been attempted by different workers with varying success and described below:

3.1 Photoperiod management

Improving estrus synchronization protocols is important, particularly to ensure that protocols which guarantee reduced use of hormones and environmental safety also result in acceptable reproductive efficiency [20]. Owing to the low variations of photoperiod in subtropical latitudes, as well as the marked seasonal variations in food availability for animals maintained in extensive conditions, suggested that some breeds have developed a weak response to photoperiodic inhibition of reproduction. In these so-called ‘photoperiodic flexible breeds’, nutrition plays a major role in controlling the annual cycle of reproduction. In artificial photoperiod conditions, short days can stimulate reproductive activity whereas long days can inhibit it. In fact, in subtropical female goats subjected to alternations between three months of long days (14 h of light/day) and three months of short days (10 h of light/day), ovulations invariably start during short days and end during long days.

The artificial alteration in the day light has been used in past for control of ovarian cyclicity in ewes with varying success. The artificial production of short photoperiod during the summer season requires a special daylight-proof housing which is not economical to poor or marginalized small ruminant farmers. However, artificial constant short days from the winter solstice do not prevent the end of the breeding season. Similarly, artificial constant long days from the summer solstice do not prevent the onset of the breeding season. These results suggest that the seasonal cycle of reproductive activity in both females and males is driven by an endogenous annual rhythm that is synchronized by photoperiod. The existence of an endogenous reproductive rhythm has been supported by several studies where animals exposed to constant short or long days or equinoctial photoperiod displayed alternation between periods of rest and sexual activity. The existence of this endogenous cycle has two main consequences in terms of practical applications of photoperiodic treatments. First, animals cannot be maintained in permanent activity by the application of a short stimulatory photoperiod because they become refractory to this daylength. Second, to avoid the establishment of refractoriness, animals must perceive alternations between long and short days. Photoperiodic information is conveyed through several neural relays from the retina to the pineal gland where the light signal is translated into a daily cycle of melatonin secretion: high at night, low during the day. The attempts of alteration in the photoperiod were found to be less successful in ewes due to their pronounced reproductive seasonality and also not commonly used at the commercial farms because of the anticipated costs and wide range of responses to the programmes in sheep.

3.2 Male effect

Ewes and ram are sensitive to their social environment, which can be used to manage their reproductive cycle. The so-called male effect is a technique to stimulate the sexual activity in seasonally anovulatory ewes [21]. The male effect is the most ancient farmer’s practice for out-of-season breeding in sheep and goats. Basically, a flock of females in anestrus is exposed to sexually active males, which triggers LH secretion and synchronized ovulations [10, 29] concluded that presence of male in the group of ewes produces some behavioral signals that trigger LH secretion leading to ovulation and resumption of the cyclical ovarian activity. However, its practical use is limited by the variability of ovulatory responses between breeds and seasons. The male effect may induce ovulations at any time of the seasonal anestrus in breeds exhibiting moderate seasonality. The male effect does not reliably induce sexual activity in the middle of the anestrus period and only advances the onset of the breeding season by a few weeks when applied at the end of the anestrus period [9]. However, since the 1990s, the efficacy of the male effect in highly seasonal breeds has been greatly improved with the development of photoperiodic treatments. Currently, males or both males and females are subject to photoperiod manipulation, with or without melatonin administration. This treatment leads to reactivation of the male gonadal axis and boosts the success of the male effect in these very seasonal breeds [21]. On-farm, male effect implementation is typically associated with out-of-season natural mating to synchronize births in both goats and sheep, without using progestagens. One concern with the use of the male effect in AI programs is that it may first trigger an infertile short ovulatory cycle, followed by a second normal (i.e., fertile) cycle. Most female goats have a short ovarian cycle of 5–7 day-length following the introduction of bucks, followed by a second ovulation associated with estrus behaviour and a normal luteal phase [6]. The consequence is the occurrence of two peaks of fecundation over a period of 2 weeks. Pre-treatment of females with progestagens or progesterone is the only practical way of obtaining a single peak of conception when using the male effect. One of the major factors affecting the efficacy of response to the male effect depends on the strength of seasonality of the female and male ewes. In this respect, the response to the male effect varies within breeds through the seasonal anestrus period, and among breeds from different latitude origins. Introduction of the male may induce highly fertile ovarian activity in anovulatory goats throughout the year. In contrast, when used alone in highly seasonal breeds, the male effect can only advance the onset of the breeding season by a few weeks; it does not satisfactorily induce full sexual activity in the middle of the anestrus period.

Depending on breed and/or on anestrus period, the pre-treatment of females and/or males with photoperiod may be necessary to optimize the response to the male effect. The treatment of males and females with artificial photoperiod is necessary to improve the response to the male effect. Under these conditions, most does exposed to males ovulated (99%) and 81% kidded [21]. The main critical factor for success of the male effect is the use of sexually active males. Bucks, but not females, are thus treated with long days followed by natural days or melatonin to improve the efficiency of the male effect and can stimulate ovulation and estrus behaviour in female goats better than untreated males. Availability of sexually active males allows producers to manipulate the annual breeding season according to consumer demands, without the restraint of also keeping females in confinement for teasing.

4. Conclusion
Sheep is a short day breeding animal and the reproductive physiology is regulated by several factors including ambient temperature, photoperiod, melatonin and thyroid nutrition hormones, vicinity of male, inter-current diseases and intervention by hormonal approaches.

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