

# Uterine Involution and Ovarian Activity in Postpartum Holstein Dairy Cows. A Review

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## Abstract

Following parturition in the cow, there is a significant period of sexual quiescence of variable length. This period of reproductive quiescence was found to be longer in suckling or intensively milked animals. This acyclic period is generally considered as the postpartum anoestrous period.

The postpartum period constitutes an important period in the reproductive life of dairy cows because of its enormous influence upon subsequent fertility. The entire postpartum period, puerperium, is defined as the period from parturition until the genital organs return to its normal physiological and histological condition, as in normal non-gravid state. They added that any extension of the puerperium in cows might have a detrimental effect on the reproductive performance of the individual animal. Thus, the main determinant of this period is essentially dependent on the resumption of normal ovarian cycles, the manifestation of estrus behaviour and conception following insemination.

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## Introduction

Puerperium in cattle is classified into three stages, early puerperium, clinical puerperium, and whole puerperium. The author added that early puerperium lasts nine days during which the placenta must be dropped either naturally or manually. Clinical puerperium stays 21 days during which the uterus returns to its normal size, but not normal histological structure. The whole puerperium lasts about 42 days during which the uterus regains its normal histological structure as before pregnancy. Depending on the endocrine status the puerperium is classified into the puerperal period, intermediate period or pre-ovulatory period and post-ovulatory period. Puerperal period extends from calving to the onset of pituitary sensitivity to GnRH at 10-12 days postpartum. The intermediate or pre-ovulatory period is the period which extends from the onset of pituitary sensitivity to GnRH until first ovulation at 20-30 days postpartum. The post-ovulatory period is the period which begins with first ovulation and lasts until complete uterine involution at 40-45 days postpartum.

The postpartum female undergoes a series of physiological and anatomical re-adjustments in both the uterus and ovaries for the restoration of her reproductive capacity. These physiological changes that occur during the puerperium, include uterine involution, resumption of ovarian function and return to cyclical activity as well as the elimination of bacterial contamination of uterine lumen that occurs during parturition.

### *Uterine Involution*

The restoration of the uterus to its normal non-pregnant size and function after parturition is termed uterine involution which depends on the rate of myometrial contractions, elimination of bacterial infection and the histological regeneration of the endometrium [1, 2, 3]. Involution of the uterus is necessary before the cow can conceive again. As a result of the removal of the fetus, oxytocin and prostaglandin  $F_{2\mu}$  ( $PGF_{2\mu}$ ) production reduced the uterine size [4]. The reduction in the size of the uterus occurs in decreasing logarithmic scale, the greatest change occurring during the first days after calving [5]. Uterine involution is considered to be complete when both

uterine horns had returned to equal or almost equal non-gravid size in their normal location in the pelvic floor, and their normal tone and consistency [6]. Uterine involution results from three overlapping processes: uterine contraction, loss of tissue and tissue repair [7].

It was found that the diameter of the previously gravid horn was halved by 5 days postpartum, and its length was halved by 15 days postpartum [8]. The uterine involution is noticed to begin rapid then the subsequent changes are slower. The reduction in the rate of involution between four to nine days postpartum, with a period of accelerated changes from day ten to fourteen, and gradual decrease thereafter [9]. Moreover, Elmetwally et al. (2016) reported a complete involution of a uterus in dairy cows within forty to fifty days postpartum [2]. However, there is some dispute about the complete uterine involution and the differences are probably only subjective. It was reported that in dairy cattle the time taken for complete uterine involution ranged from 26 to 52 days [5]. This variability of more or less inaccurate criteria, as well as plenty of endogenous and exogenous factors, affects the involution rate [10]. The reduction of uterine size occurs as a result of vasoconstriction of blood vessels in association with myometrial contraction in a logarithmic scale with major changes occurring during the first few days after calving. They added that postpartum uteri were found to contract to a half of gravid length at 15 days and the weight of the uterus decreased from 9 kg at parturition to 1.0 kg at 30 days postpartum [7].

Prostaglandins have a role in controlling uterine involution [11]. A positive correlation between  $PGF_{2\mu}$  metabolites concentration in puerperal circulation and the diameter of a uterine horn was recognized. Using exogenous  $PGF_{2\mu}$  twice daily for 10 days starting from day 3 postpartum, uterine involution has been accelerated by 6-13 days [12].

After shedding of the allanto-chorion, the caruncle is about 70 mm long, 35 mm wide and 25 mm thick. The endometrial crypts frequently contain remnants of the chorionic villi, which were detached from the rest of the allanto-chorion at the time of placental separation. Within the first 48 hours postpartum, there is evidence of early necrotic changes in the septal mass of the caruncle, the caruncular blood

vessels become rapidly constricted and are nearly occluded. By 5 days of postpartum, the necrosis proceeds rapidly, so that the stratum compactum is now covered by a leukocyte-laden necrotic layer. Some of this necrotic material starts to slough and contributes to the lochia. Small blood vessels, mainly arterioles, then protrude from the surface of the caruncle, from which there is oozing of blood, causing a red coloration of the lochia. By 10 days after calving, most of the necrotic caruncular tissue sloughs and undergoes some degree of liquefaction, and by 15 days postpartum sloughing is completed, leaving only stubs of blood vessels protruding from the exposed stratum compactum. This eventually becomes smooth by day 19, owing to the disappearance of the vessels [13, 3].

Regeneration of the epithelium of the endometrium occurs immediately after parturition in those areas which were not seriously damaged and is completed in the inter-caruncular areas by day 8. Complete re-epithelialization of the caruncle, which is largely derived from the centripetal growth of cells from the surrounding uterine glands, is accomplished from 25 days onwards, although the stage at which complete healing occurs is variable. Whilst these changes are taking place the caruncles are becoming smaller so that at 40-60 days they consist of small protrusions 4-8mm in diameter and 4-6mm high. They also differ from those of nullipara because they are larger and have melanin pigmentation and a more vascular base [5, 14].

The uterine cervix constricts rapidly postpartum, within 10 to 12 hours it becomes almost impossible to insert a hand through it into the uterus and by 96 hours it will admit just two fingers [13]. The cervix also undergoes atrophy and shrinkage due to the elimination of fluid and the reduction of muscle tissue. The mean external diameter is 15cm at 2 days, 9-11 cm at 10 days, 7-8 cm at 30 days and 5-6 cm at 60 days postpartum. A useful guide that involution is occurring normally, is to compare the diameter of the previously gravid horn with that of the cervix since at about 25 days postpartum, the latter starts to exceed the former [5].

#### *Factors Affecting Uterine Involution*

##### *Season*

For the uterine involution, it was found

that involution is probably most rapid in spring and summer [5]. The season of parturition might also affect the length of puerperium as in summer and autumn the uterine involution takes a longer time than in winter and spring [1]. Other workers did not find any significant correlation between season and rate of uterine involution [2].

##### *Nutrition*

Regarding the effect of nutrition on the uterine involution [6], it was reported that over conditioning of animals during dry period was associated with excess fattens and increases of body condition score (BCS) >4, which are associated with difficulties at parturition with subsequent delayed uterine involution and retention of the placenta. However, Gordan (1996) illustrated that too fat cows at calving have a reduced appetite in early lactation and mobilize an excessive amount of body fat, which may have an adverse effect on reproduction [15]. The excessive protein intake in the diet increased urea levels in the body, particularly in the uterus and reduces pH [16]. Urea stimulates the production of prostaglandin F<sub>2α</sub> which reduces the viability of the embryo. Moreover, high protein also appears to reduce progesterone which may result in poor fertility.

##### *Milk Yield*

The milk yield has an influence on uterine involution. Of notes, the increase of milk yield delayed uterine involution [17, 2]. On the contrary, there are some studies that reported that uterine involution occurred sooner in postpartum cows that had higher milk yields [18, 2].

##### *Age*

The age and parity have an influence on postpartum uterine involution. It has been reported that pluriparous cows needed a longer time for completion of uterine involution than primiparous ones [19, 2]. On the other hand, the rate of uterine involution was faster in pluriparous cows than primiparous ones [20]. However, other studies reported that the age of the cow did not affect the rate of uterine involution [21]. Now, it is quite clear that any disturbance occurs in the postpartum period as retained fetal membrane [6], mastitis [22], Puerperal metritis [6], delayed uterine involution [2, 6], claw affections and metabolic disorders such as milk fever results in postpartum infertility [23]. The uterine

infection usually delays uterine involution and the conversion of the normal flora of the female genital tract from a commensal to pathogenic is associated with a number of predisposing factors such as suppression of the host defense mechanism, stress of pregnancy, parturition, and lactation in addition to antibiotic or steroid therapy [24]. Moreover, the immuno-stimulant drugs were found to improve the puerperal condition in dairy cattle [25]. The restoration of ovarian acyclic activity after calving play an important role in the uterine defense mechanisms to prevent invading of bacteria from colonizing the uterus and delay the completion of uterine involution as well as causing harmful effects on the reproductive efficiency of the cow [25].

#### *Postpartum Ovarian Activity (Ovarian Rebound)*

Resumption of the postpartum ovarian activity is required early to achieve normal fertility and acceptable calving interval [1]. The series of events leading to estrus and ovulation in postpartum cows are similar to that of normal cyclic cows [26] and are very dependent upon a fully functional hypothalamic-pituitary interaction. Pregnancy interrupts the cyclic interplay between the hypothalamus, adenohipophysis, and gonads because secretion of large quantities of the placental steroids, that exert a continuous negative feedback effect (progesterone) and deplete pituitary store of LH (estradiol) towards the end of pregnancy [27]. Thus, resumption of ovarian cyclicity depends upon the recovery rate of the hypothalamus-pituitary interaction that appears to occur in three distinct phases [28]. The first phase begins 2-4 weeks after parturition and is characterized by repletion of anterior pituitary store of LH. The depletion/repletion cycle of anterior pituitary LH is clearly a major limiting factor for early postpartum recovery [29]. The second phase is related to an increase in the sensitivity of the hypothalamus to the positive feedback effect of estradiol [30]. The third phase of recovery requires an escape from the effects of suckling. The inhibitory action of pregnancy on follicular development in cow continuous after calving by a mechanism postulated to involve the previously gravid uterine horn and/or the ovary bearing the corpus luteum of pregnancy [31]. Of notes, the corpus luteum of pregnancy and/or conceptus inhibits the growth rate of the antral follicles even after parturition [32]. This

inhibitory action continues for about 20 days postpartum and reduces the frequency of ovulation from the ovary ipsilateral to the previously gravid uterine horn [33].

The uterus is also involved in controlling the postpartum ovarian function [34]. The uterus exerts an influence on ovarian activity since it has been known for some time that in the majority of postpartum cows, ovulations occur in the ovary contralateral to the previously gravid horn [13]. It has also been shown that prostaglandin metabolite usually returns to normal levels before the first postpartum ovulation. Similarly, the ovario-uterine axis exerts an inhibitory effect on pituitary LH secretion during the early postpartum period, experimental hysterectomy results in a rapid increase in plasma gonadotropin concentration [35]. Also, the adrenal cortex plays an important role in the return of postpartum estrus.

Opinion varies about the time of the first postpartum estrus [36]. The first postpartum estrus occurred at  $17.4 \pm 0.8$  days [33], 30 days, 32 days [37], 33 days [38] and was 30-76.3 days for dairy cattle [9]. In addition, different wide ranges were reported for the first postpartum estrus 6-55 days [39]

The follicular growth was detected in the early postpartum period at about 4 to 5 days postpartum [40]. The follicular activity by rectal palpation was investigated at 7 to 10 days postpartum in all normal cows. The ovarian changes occur every 4 days during the postpartum period in dairy cows and the mean interval from parturition to the appearance of ovarian follicles (0.5 to 1.0cm in diameter) was  $15.0 \pm 0.2$  days in normal cows [40]. Moreover, the average number of small follicles (3 to 5mm diameter) is decreased by day 25 postpartum and the number of large follicles (10 to 15mm or more than 5mm in diameter) is increased with increasing postpartum days [41].

#### *Factors Affecting the Postpartum Ovarian Activity Parturition*

Parturition is usually followed by a normal physiological quiescence period and the length of this period is variable and can be affected by many factors such as nutritional status, body condition score, suckling vs milking, periparturient abnormalities, milk yield, season, age, parity, stress, infection and other

environmental factors [34, 15].

### *Nutrition*

The reproduction is a complex of events where management, nutrition, stress, diseases, environmental condition, toxins, and other factors may all interact to affect its performance. Thus, we are learning more about how nutrition interacts with reproduction, so that we may be better able to manage nutrition and feeding to improve the reproductive performance, [2]. The art of feeding dairy cattle is rapidly becoming the basic and applied science of dairy cattle nutrition. Because dry cow feeding and management set the stage for both production and reproductive performance after parturition, dairymen are more concerned with dry cow feeding and management practices that enhance the performance [42]. Poor nutrition status before the beginning of the postpartum period accentuates the need for adequate nutrition during this period. Consequences of inadequate or improper nutrition before the beginning of postpartum period include delayed postpartum estrus, silent estrus, delayed ovulation, decreased ovulation rate and increased embryonic mortality [43, 44]. Adequate nutrition during the postpartum period is even more critical in primiparous cow because of nutritional requirements for growth, in addition to those for lactation during the postpartum period [43].

Moreover, various minerals including microelements can influence the reproductive performance of dairy cattle [45]. It was found that calcium as an individual nutrient has been associated with poor production when severely deficient [46]. Cows fed high calcium and vitamin D diet had more rapid uterine involution, fewer days to first service and fewer days open [2]. Also, a deficiency of phosphorus has the same effect as the calcium-phosphorus ratio should be maintained at 2:1 [9]. Deficiency of sodium and a correlated excess of potassium can reduce fertility by irregular estrous cycle, endometritis and follicular cysts [46]. The author added that silent heat, delayed ovulation, follicular and luteal cysts, and embryonic mortality may result from vitamin A deficiency. The importance of energy balance on normal postpartum ovarian cyclicity in high producing dairy cattle has been recognized in several studies [47, 48, 2].

### *Suckling*

Suckling is considered an exteroceptive stimulus that plays a major role in governing reproductive cycles in female mammals [49]. The first ovulation and first estrus tend to occur earlier in dairy than in beef suckler cows [15].

Relative to suckling animals, the onset of ovulation and estrous cycle are also delayed in milking cows. High yielding cows tend to stop cycling spontaneously or exhibiting a longer cyclic period, [50]. There is a high correlation between the times taken for energy balance during early lactation and first ovulation. Dietary energy restriction, undernutrition and/or poor body condition exacerbates the effect of suckling and markedly extends the postpartum anovulatory period, [51].

### *Postpartum Disturbances*

The whole range of periparturient problems delayed ovarian rebound [5]. Endometritis developed as a result of untreated retained placenta did not affect the early resumption of ovarian activities despite retarded uterine involution and large quantities of purulent vaginal discharge [52, 53]. This may be related to the reduced intensity of stress, which may be aggravated by manual interference and traumatic delivery experienced during placental removal [54]. Furthermore, cows with stillbirth and vaginal prolapse showed an increase in open days, the number of inseminations required per-conception and calving interval resulting in heavy economic losses [55]. Indeed, dystocia had both direct and indirect sparing association with poor reproductive performance [56, 57].

### *Metabolic Diseases and Season*

Regarding the metabolic diseases, it was found that milk fever increases the uterine involution period and number of service per conception. Also, seasonal variations were found to have an influence on postpartum ovarian activity [2]. seasonal variations in conception rate and a longer interval between parturition and first estrus (The service period) was investigated in winter and early spring [58]. Moreover, spring – calving dairy cows have been reported to have a longer period between calving and first ovulation than autumn calving ones [2].

### *Age or Parity*

The age of parity did not affect the resumption of ovarian activity [59] although primiparous may have a longer interval than multiparous cows [5]. Between 33 and 60 months of age, younger cows had their first ovulation earlier than older ones [18]. An increase of acyclic period after calving was observed to be more frequent among both heifers and cows after their fourth calving [2]. Multiparous cows showed postpartum ovarian activity at an earlier stage of the postpartum period than primiparous cows [60].

### *Effect of Some Drugs on Postpartum, Uterine Involution and Postpartum Ovarian Rebound:*

#### *Use of Prostaglandin F<sub>2μ</sub> during Early Puerperium*

Prostaglandin F<sub>2μ</sub> appears to be the normal physiological signal whereby the uterus causes regression of the corpus luteum at the end of the estrous cycle. The PGF<sub>2μ</sub> is important for uterine involution and ovarian function. The duration of increased PGF<sub>2μ</sub> production in the postpartum period negatively correlated with the number of days to complete uterine involution and the interval between parturition and resumption of normal ovarian activity [61]. Therefore, PGF<sub>2μ</sub> may be implicated in the resumption of the postpartum ovarian activity [62].

Ovarian activity increased during the early postpartum period following PGF<sub>2μ</sub> administration [63]. Also, partial suppression of PGF<sub>2μ</sub> synthesis during the early postpartum period reduced ovarian activity [62]. This was attributed to the local effect of PGF<sub>2μ</sub> on the hypothalamic-pituitary axis and increased LH pulse frequency [64]. The use of PGF<sub>2μ</sub> between 14 and 28 days postpartum shortens the interval to the first or subsequent estrus and re-establishment of estrous cycle becomes earlier to the normal duration [65, 66]. Furthermore, the exogenous PGF<sub>2μ</sub> or uterine manipulation between 29 and 42 days after calving shortens the postpartum interval in suckled beef cows [67]. Meanwhile, it has been reported that exogenous PGF<sub>2μ</sub> administered to primiparous cows during the postpartum period does not influence the postpartum interval [68]. Of notes, estrus induced by PGF<sub>2μ</sub> injected at 24 days postpartum results in a cleansing effect on the uterine environment and increases conception rate [65]. Pankowski et al. (1995)

hypothesized that the use of PGF<sub>2μ</sub> replacing reproductive programs based on routine rectal palpation and intrauterine therapies would result in cost-effective reduction in days open and improving reproductive efficiency [69]. Also, the days open were fewer for cows treated with prostaglandin F<sub>2μ</sub> [70]. The administration of PGF<sub>2μ</sub> once between days 14 and 18 post-calving resulted in a reduction in days open [71, 72]. Moreover, the pluriparous dairy cows treated with PGF<sub>2μ</sub> on day 8 after calving had shortened postpartum interval and reduced days open [73]. Additionally, Lopez-Gatius (2003) and others observed a decreased days open (56.6±5.7 days) than the control group (57.1±7.8 days) after administration of PGF<sub>2μ</sub> during the early postpartum period [74, 70]. On contrary, some other studies reported prolonged days open in PGF<sub>2μ</sub> treated cows than in normal cows [75, 76, 77].

The number of services per conception was found to decrease when PGF<sub>2μ</sub> given once between days 14 and 18 post-calving [72, 77]. It is generally accepted that fertility, in term of conception rates, of heifers after PGF<sub>2μ</sub> treatment is not impaired if compared to untreated control animals inseminated at a natural estrus [78]. At the same time, the single injection of PGF<sub>2μ</sub> between days 14 and 28 post-calving increases the conception rate [71, 79]. On the other hand, some studies found lower conception rates associated with exogenous PGF<sub>2μ</sub> administration [80, 81].

#### *Uses of GnRH during Early Puerperium*

Some suggested, the reproductive goals of GnRH treatment for dairy cows were: 1- to start cycling by 3 weeks postpartum, 2- to have their uteri involuted and infection free by 4 weeks postpartum, 3- to express estrus behaviour at their second cycle and each cycle afterwards until bred and to conceive at first breeding 50-85 days postpartum [82].

Schams et al. (1973) reported that in 6 cows with a plasma progesterone level less than 1 ng/ ml treated with 1.5 mg GnRH during the postpartum period (days 12-18), follicular development could be observed in their ovaries at the same day of GnRH injection with ovulation one day later [83]. At the same time, Britt et al. (1974) found that GnRH, administration two weeks postpartum induces LH release and ovulation [84]. Also,

a single injection of GnRH induced LH surge and ovulation when given around days 10 to 18 postpartum in dairy cows [82, 40] and around days 21 to 31 postpartum in beef cows [85, 86] but not before these days [87]. A single injection of GnRH induces luteal structures in 75% of acyclic cows [88]. Two injections of GnRH 10 days apart also induce cyclic activity in beef cows [89] but not affect mean calving interval [34]. Ovulation of well-developed follicles is induced by GnRH [90].

Intermittent injections of a small dose of GnRH intravenous every 2 hours to postpartum cows have been reported to induce LH pulses and terminal maturation of the dominant follicle. In dairy cows, intermittent GnRH injections before day 8 postpartum induced LH pulses and increased concentration of estradiol-17B in circulation [34]. Moreover, Benmard and Stevenson (1986) reported that treatment with GnRH (200ug) between 10 and 14 days postpartum reduced the interval to first ovulation and first detected estrus and increased the proportion of cows with three or more ovulations before the first service from 57% of saline-treated controls to 83% [72].

The interval from calving to conception is influenced by both the interval between calving and insemination and the fertility of an insemination [84]. Furthermore, the administration of GnRH to dairy cows less than 40 days postpartum significantly ( $p < 0.01$ ) reduces the number of days open by 2.75 days [91]. On the other hand, some studies investigated the non-significant effect of GnRH administration on days open and reproductive performance in dairy cows [65, 92].

The effect of GnRH on the fertility of inseminations in the post-calving period was assessed by examining the number of services per conception. A significant reduction in the number of services per conception by 0.05 services was noticed with GnRH administration between days 13 and 28 postpartum [91]. Also, a significant reduction in the number of services per conception was reported when GnRH was given between days 10 and 18 postpartum [72]. On the other hand, some authors recorded no effect of GnRH administration on the number of services per conception [65, 93]. The

conception rate was increased once with GnRH treatment between days 13 and 18 postpartum [91]. The same effect was reported when GnRH was given between days 10 and 18 postpartum [94].

#### *Uses of GnRH plus PGF<sub>2μ</sub> during early puerperium*

It is generally believed that the postpartum anoestrus is caused by the deficiency of gonadotrophic hormones LH and FSH owing to its ability to stimulate the release of LH as well as FSH. The gonadotrophic releasing hormone (GnRH) has been successfully used in combination with prostaglandin F<sub>2μ</sub> to induce ovulation in anoestrus and early postpartum cows [84, 95]. Benmard and Stevenson (1986) administered GnRH and PGF<sub>2μ</sub> ten days apart with no benefit on reproductive performance except for the reduced number of services per-conception in cows with normal health status [72]. Moreover, the use of GnRH seven days prior to synchronization of estrus with PGF<sub>2μ</sub> can alter the follicular development as the treatment with GnRH produces preovulatory follicle which is more homogenous, more estrogen active, more dominant and there is a greater size difference between the pre-ovulatory and subordinate follicles prior to estrus [96]. The negative effects of GnRH and PGF<sub>2μ</sub> were unexpected [92]. On the other hand, the administration of GnRH on day 15 postpartum increased the incidence of pyometra and pre-breeding anoestrus unless the cows were treated 10 days later with PGF<sub>2μ</sub> analog (cloprostenol) [65]. Additionally, the administration of GnRH and PGF<sub>2μ</sub> did not improve postpartum reproductive performance except for a reduced number of services per conception [72, 97]. Decreased number of services per conception with GnRH and PGF<sub>2μ</sub> treatment was investigated in some studies. Exogenous PGF<sub>2μ</sub> facilitates the ability of exogenous GnRH to release Pituitary LH in multiparous and primiparous dairy cows with subsequent decreased number of services per conception and conception rate [97].

Altogether, the changes which are present during the postpartum period in dairy cows play a crucial role in the determination of future fertility and productivity of the dairy herd. Further, the administration of prostaglandins and gonadotropins may

improve the postpartum reproductive performance in dairy cows.

### Conflict of Interest Statement

The authors declare no competing financial interests.

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