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Nutritional Factors That Regulate Ovulation of the Dominant Follicle During the First Follicular Wave Postpartum in High-producing Dairy Cows

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Abstract. During recent decades, milk production per cow has increased drastically due to improved management, nutrition, and genetic selection; however, the reproductive performance of high-producing dairy cows has been declining. One of the factors responsible for this low reproductive performance is negative energy balance (NEB). NEB affects the onset of first ovulation in early postpartum cows. It is generally accepted that early first ovulation positively relates to the resumption of normal ovarian function, first service, and conception rate in dairy cows. Hence, delayed first ovulation has a negative impact on subsequent fertility. The metabolic condition of cows in NEB shifts to catabolic metabolism, which in turn causes increased plasma growth hormone and non-esterified fatty acid concentrations and decreased plasma insulin-like growth factor-1, insulin, and glucose concentrations. On the other hand, plasma β-carotene concentrations decrease throughout the dry period and reach their nadir in about the first week postpartum, and this change reflects energy balance during the peripartum period. β-Carotene plays a role independently of vitamin A in the reproductive performance of dairy cows, and the positive relationship between supplemental β-carotene and reproductive function has been demonstrated in many studies during the past decades. However, β-carotene content in corn silage, which is a popular main feed in high-producing dairy cows, is very low. This review describes nutritional factors related to ovulation during the first follicular wave postpartum in dairy cows.

Keywords: β-Carotene, Dairy cow, First follicular wave postpartum, First ovulation, Metabolic hormone

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Milk production per cow has steadily increased due to improved management and genetic selection. In the United States, the milk yield in Holstein cows has increased by approximately 20% in the last 10 years [1]. In Hokkaido, Japan, the milk yield in Holstein cows has increased from 7,114 kg/305 days in 1985 to 9,053 kg/305 days in 2008 (Livestock Improvement Association of Japan). However, reproductive efficiency (e.g., calving interval, services per conception) has declined with the increase in milk production. For example, days open in Hokkaido have prolonged from 116 days in 1985 to 147 days in 2008 (Livestock Improvement Association of Japan). Likewise, in the United States, Butler [2] presented data showing a decline in first-service conception rate from approximately 65% in 1951 to 40% in 1996. A decline in reproductive efficiency in the modern dairy cow is not only occurring in Japan and the United States. Equivalent decreases in conception rate at first service have been reported in Ireland [3], the United Kingdom [4], and Australia [5]. Therefore, modern high-producing dairy cows have lower reproductive performance compared to those in the preceding decades.

Although nutritional management has improved for high milk production, modern high-producing dairy cows undergo a period of severe negative energy balance (NEB) during early lactation. Because energy output via milk production exceeds energy intake via feed consumption, postpartum dairy cows have to resume normal ovarian cycles under NEB to optimize fertility during the postpartum period. However, recent reports in the scientific literature confirm trends for significantly longer intervals to first ovulation in postpartum dairy cows [6, 7].

It is generally accepted that cows with early resumption of ovarian function have higher fertility [8–10]. We observed previously that the recovery of ovarian function and subsequent reproductive performance by 3 weeks postpartum were superior in ovulatory cows to those of anovulatory cows [11]. Namely, this ovulation could be an early index of recovery of normal ovarian function and subsequent reproductive performance in dairy cows.

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However, the factors that control the first ovulation postpartum have not been fully elucidated. This review reveals that postpartum ovarian activity, lactation characteristics, and nutritional factors relate to ovulation during the first follicular wave postpartum in high-producing dairy cows.

Postpartum Ovarian Activity and Changes of Reproductive Hormones

In most dairy cows, several follicles appear by 5 days postpartum and a dominant follicle develops by 10 days postpartum [12, 13]. Approximately half of all cows ovulate at the first follicular wave postpartum [6, 10, 14]. However, in the other half, the dominant follicle during the first follicular wave postpartum becomes atretic or cystic, and the first ovulation occurs at about the fourth follicular wave after calving [15, 16]. In our previous study, we used color Doppler ultrasonography to monitor local blood flow during the growth of individual follicles in the first follicular wave postpartum [17]. The dominant follicle of the first follicular wave appeared at 7 days postpartum, and a dominant follicle with a diameter of approximately 10 mm and blood flow was observed by 14 days postpartum regardless of ovulation or anovulation (Fig. 1). In the ovulatory cows, a CL with blood flow was observed by 17 d postpartum (Fig. 1). On the other hand, the dominant follicle of the anovulatory cows continued to grow and maintain identifiable blood flow (Fig. 1). Thus, the rate of follicular growth did not differ between the ovulatory and anovulatory cows during the postpartum period, and local blood flow was detected in the dominant follicles of all cows despite ovulation or anovulation. Angiogenesis, the formation of a new network of blood vessels, is essential for follicular development and ovulation [18, 19]. In addition, a recent report suggests that the angiopoietin–tie system that acts on angiogenesis in concert with vascular endothelial growth factor controls the blood vessels to maintain active angiogenesis in developing bovine follicles [20]. The maintenance of follicle vasculature and appropriate blood supply to the large follicles is essential for follicle dominance [21]. However, an insufficient blood flow supply is not the cause of anovulation during the first follicular wave postpartum.

Follicle stimulating hormone (FSH) appears to be insensitive to metabolic status [22, 23]. The plasma FSH concentration did not differ between the ovulatory and anovulatory cows until 14 days postpartum in our study [17]. On the other hand, the plasma estradiol-17β (E2) concentrations during the growth of the dominant follicle at the first follicular wave postpartum increased only in the ovulatory cows, while those in the anovulatory cows did not change [17, 23, 24]. Moreover, luteinizing hormone (LH) pulse frequency was reported to be greater in ovulatory cows than that in anovulatory cows [22, 25, 26]. Detailed endocrine profiles in ovulatory and anovulatory cows during the first follicular wave postpartum reveal that ovulatory cows show increased plasma E2 with follicular growth followed by an E2 peak, LH surge (approximately 21 ± 7 h after the E2 peak), and ovulation (Fig. 2) [17]. On the other hand, an E2 peak and LH surge could not be confirmed in the anovulatory cows (Fig. 2) [17]. Thus, it is likely that an insufficient ability of granulosa cells to secrete E2 is a determinant for anovulation rather than insufficient angiogenesis.

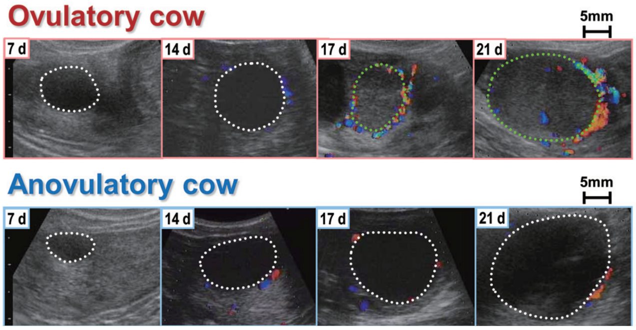

Fig. 1. Representative images of dominant follicles during the first follicular wave postpartum of ovulatory and anovulatory cows. Red represents blood flow towards the transducer, and blue indicates blood flow away from the transducer. The color gain of the flow mode was set to detect movement of at least 2 mm/sec. Scale bars represent 5 mm. White dotted lines indicate follicular margins, and green dotted lines delineate margins of the corpus luteum. Modified from Kawashima *et al*. (2007) [17].

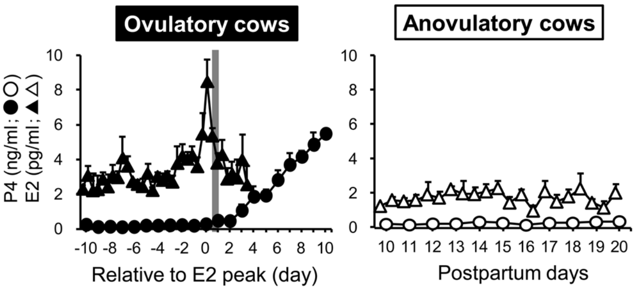

Fig. 2. We obtained blood samples 4 times/day for detection (presence or absence) of an LH surge, 2 times/day for detection of an E2 peak, and 1 time/day for the P4 profile. E2 concentrations are shown at 12 h intervals from 10 d before to 10 d after the E2 peak in ovulatory cows (n = 5) and from 10 d to 20 d postpartum in anovulatory cows (n = 4) (mean ± SEM). E2 concentrations are indicated by triangles and P4 concentrations are indicated by circles—solid in ovulatory cows and open in anovulatory cows. The gray vertical bar in the graph for ovulatory cows indicates the range of the LH surge (21 ± 7 h after the E2 peak). Modified from Kawashima *et al*. (2007) [17].

The Relationship Between Lactation Curve and Ovulation During the First Follicular Wave Postpartum

A previous study showed that NEB was directly related to the postpartum interval to the first ovulation and that differences in energy balance were reflected in the milk yield [27]. In contrast, another study showed that cows having delayed resumption of luteal activity had greater NEB between the first and second week postpartum compared with cows displaying early luteal activity despite not differing in milk yield [28]. Therefore, NEB is not always affected by milk yield but relates to the resumption of estrous cycles. However, there is little information about the relationship between the milk yield and the resumption of postpartum ovarian function.

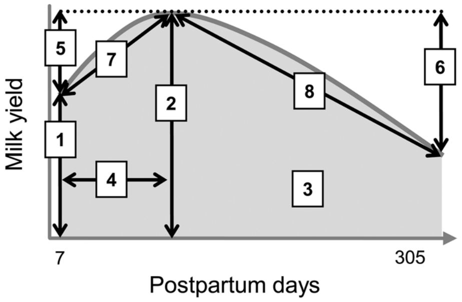

Fig. 3. The lactation curve was characterized by 8 indexes based on the weekly average of milk yield as follows: (1) the 1st-week milk yield, (2) the peak milk yield, (3) the actual 305-day milk yield, (4) the peak week, (5) the difference in milk yield between 1st week and peak week, (6) the difference in milk yield between peak week and last week (43rd week postpartum), (7) the proportional increase in milk yield between week 1 postpartum and the week of peak yield, and (8) the proportional decline in milk yield between the week of peak yield and the last week. Modified from Kawashima *et al*. (2007) [29].

Thus, we examined the relationship between characteristics of the lactation curve, based on daily milk yield, and ovulation during the first follicular wave postpartum in dairy cows (Fig. 3) [29]. Consequently, the weekly increase in milk yield between the first and peak weeks (Fig. 3, index 7) in the ovulatory cows during the first follicular wave postpartum was less than that in the anovulatory cows (1.71 kg/week *vs.* 2.54 kg/week), although total milk yield did not differ between the ovulatory and anovulatory cows [29]. NEB usually reaches its nadir during the first or second week postpartum [27]. We hypothesize that the association between energy status and increased weekly milk yield during early lactation, despite comparative first-week and peak milk yield, may be associated with anovulation during the first follicular wave postpartum. It is proposed that the lactation curve may be utilized as a simple model to evaluate the physiological environment for the resumption of normal ovarian cycles in postpartum cows. Theoretically, an acute increase in milk yield in anovulatory cows appears to induce a drastic NEB during early lactation as compared to ovulatory cows. Further studies are necessary to investigate in detail the relationship between energy balance and the proportional increase in milk yield during early lactation.

The Change of Nutritional Status During the Peripartum Period and the Relationship Between Metabolic Factors and Ovulation During the First Follicular Wave Postpartum

The late pregnancy period, parturition, and lactation have drastic effects on metabolism in dairy cows during the peripartum period. A gradual decline in dry-matter intake begins 3 weeks prepartum, with the most dramatic decrease occurring during the final week prepartum [30, 31]. Thus, metabolic hormone concentrations before parturition change to promote glucogenesis and mobilization of adipose tissue to provide sufficient energy for the fetus and mammary gland development [32]. Mobilized adipose tissue provides energy in the form of non-esterified fatty acid (NEFA) [33]. Elevation of plasma NEFA concentrations occurs from 10 days prepartum to parturition [31, 33]. Thereafter, plasma NEFA concentrations are maximum at parturition due to the stress of calving and decrease rapidly after parturition, but concentrations remain higher than they were before calving [33]. A greater degree of fatty acid mobilization during the peripartum period, as indicated by evaluated plasma NEFA, is related to greater incidences of fatty liver and ketosis [34]. Plasma concentrations of growth hormone (GH) secreted from the pituitary increase from late gestation and an acute surge is observed at parturition [35]. GH acts on adipose tissue to stimulate lipolysis, namely, tissue mobilization is driven by increases in the rate of secretion of GH [36, 37]. Furthermore, in the physiological states of undernutrition and early lactation, the liver becomes GH resistant [38, 39]. The GH receptors in the liver are downregulated, and the normal stimulatory action of GH on the synthesis of insulin-like growth factor-1 (IGF-1) in the liver becomes uncoupled. Therefore, plasma concentrations of IGF-1 decrease from about 3 weeks prepartum to 3 weeks postpartum despite the increase in GH [37, 40, 41]. Plasma concentrations of insulin from the pancreas decrease before and after parturition except for an acute surge at parturition [40, 42]. Insulin plays a central role in the homeostatic control of energy metabolism and its concentration is positively correlated with energy intake [43]. In addition, plasma glucose concentrations decrease until about 2 weeks postpartum [37, 44]. Thus, the metabolic status changes dramatically during the peripartum period in dairy cows and affects ovarian function.

Many studies have described the effect of metabolic hormones on ovarian function in dairy cows. Treatment with exogenous GH has a significant effect on ovarian follicle development [45, 46] and CL function [47] in cattle. Although GH receptor mRNA is not detected in bovine follicles, large luteal cells of the bovine CL express GH receptor and respond to GH treatment [47]. Thus, GH does not always act directly on ovarian function but interacts with other metabolic hormones. On the other hand, IGF-1 and insulin receptor mRNA were detected in bovine follicles [48–50] and luteal cells [51, 52]. Hence, IGF-1 and insulin directly stimulate both proliferation and steroidogenesis in bovine granulosa cells. Moreover, significantly increased IGF-1 and insulin concentrations are associated with ovulation [53–55]. Further, the changes in the concentration of metabolites such as glucose and NEFA in serum is reflected in the follicular fluid of the dominant follicle; hence, NEB after parturition may affect the quality of both the oocyte and the granulosa cells [56]. A recent study has shown that higher plasma NEFA concentrations during the peripartum period are associated with delayed ovulation in postpartum dairy cows [57]. Therefore, it is likely that the changes in these metabolic factors during the peripartum period alter the pattern of ovarian follicle growth and development, resulting in reduced reproductive performance in dairy cows. In fact, liver-derived IGF-1 is a factor regulating the final maturation of the dominant follicle during the first follicular wave postpartum [23], and circulating IGF-1 in ovulatory cows at the first follicular wave postpartum is higher than that in anovulatory cows regardless of parity [17, 23, 58]. In addition, we investigated in detail the time-dependent relationship

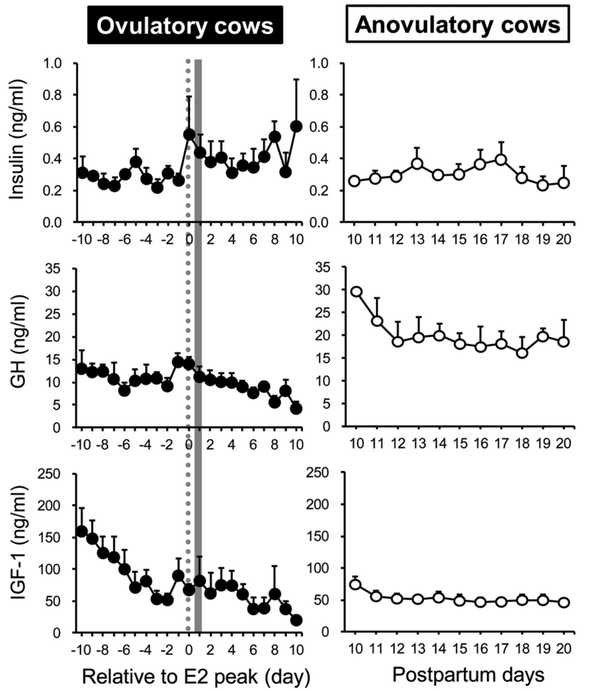

Fig. 4. We obtained blood samples 1 time/day for profiles of metabolic hormones. Solid in ovulatory (n = 5) and open in anovulatory (n = 4) cows (mean ± SEM). The dotted line in graphs of ovulatory cows indicates time of E2 peak, and the gray vertical bar indicates the range of the LH surge (21 ± 7 h after the E2 peak). Modified from Kawashima *et al.* (2007) [17].

between metabolic hormones including IGF-1, GH, and insulin and ovulation during the first follicular wave postpartum in dairy cows in early lactation by using a herd homogeneous for lactation ability [17]. In general, plasma IGF-1 concentrations in postpartum dairy cows decrease during the peripartum period when NEB is induced by limited amounts of feed intake and onset of lactation. Decreased plasma IGF-1 levels in the ovulatory cows during the first follicular wave postpartum occurred after the follicular growth phase (Fig. 4). On the other hand, IGF-1 levels in the anovulatory cows decreased before the follicular growth phase (Fig. 4). Therefore, follicular cell functions such as the steroidogenesis and proliferation in the ovulatory follicle may be stimulated by high IGF-1 levels. Subsequently, E2 secretion is stimulated, and the increase in insulin level together with the E2 peak may enhance the maturation of the dominant follicle (Fig. 4). Taken together, E2 enhanced by IGF-1 induces an LH surge and resultant ovulation of the dominant follicle in ovulatory cows during the first follicular wave postpartum. Therefore, IGF-1 is an essential factor for the growth of the dominant follicle, and insulin may stimulate the dominant follicle to mature and reach ovulation.

Thus, higher IGF-1 and insulin during the peripartum period relate to postpartum ovarian activity. Propylene glycol has been assessed to decrease the delay of the first postpartum ovulation [59, 60]; however, certain studies showed that propylene glycol treatment did not influence follicular dynamics and days to first ovulation [61] or ovulation during the first follicular wave postpartum [62]. Therefore, induction of an earlier first ovulation after parturition by improving energy status is problematic; hence, further studies are necessary to establish feeding management leading to higher IGF-1 and insulin during the peripartum period followed by the resumption of postpartum ovarian function in dairy cows.

Role of β-carotene on Ovarian Function and the Relationship Between β-carotene and Ovulation During the First Follicular Wave Postpartum

β-Carotene is abundant in pasture and good quality forage [63]; however, β-carotene content in hay and corn silage is very low [64]. In dairy cows, β-carotene plays a role in enhancing host defense mechanisms by lymphocyte and phagocyte functions, similar to vitamin A, and decreases incidence of mastitis [65] and retained placenta [66]. In addition, it functions independently of vitamin A in the reproductive performance of dairy cows, and the positive relationship between supplemental β-carotene and reproductive performance has been shown in many studies and reviewed during the past decades. The main transporters for β-carotene in the blood are high-density lipoproteins [67, 68]. The basement membrane of the blood-follicle barrier allows only the transfer of substances with a molecular weight of < 850,000 [69]. Therefore, only high-density lipoprotein-bound β-carotene can be detected in follicular fluid [70]. Moreover, the conversion rate of β-carotene to vitamin A in granulosa cells is enhanced by follicular growth, and intrafollicular concentration of vitamin A correlates positively with estradiol concentration and follicle diameter [71].

Plasma β-carotene concentrations decrease throughout the dry period and reach their nadir in about the first week postpartum; this change is similar to energy balance during the peripartum period. Thus, we hypothesized that not only the energy status but also plasma β-carotene concentrations during the peripartum period may affect ovulation in the first follicular wave postpartum in dairy cows, which led us to investigate the profiles of plasma β-carotene concentration during the peripartum period in ovulatory and anovulatory cows during the first follicular wave postpartum [72]. As a result, lower plasma β-carotene concentration during the close-up dry period was related to anovulation during the first follicular wave postpartum (Fig. 5). In addition, β-carotene supply during the close-up dry period induced ovulation during the first follicular wave postpartum in dairy cows [73]. In contrast, another study showed that β-carotene supply during the prepartum period had no effect on postpartum ovarian activity; however, β-carotene increased blood hydroxyproline, which is an indicator of uterine involution, and had a positive effect on immune function in the uterus and cervix [74]. Thus, β-carotene is one of the important nutritional factors for the resumption of reproductive function after parturition in dairy cows, and the role of β-carotene in modern high-producing dairy cows should be re-investigated.

Conclusion

This review reveals the following characteristics of nutritional status and lactation in ovulatory cows compared with anovulatory

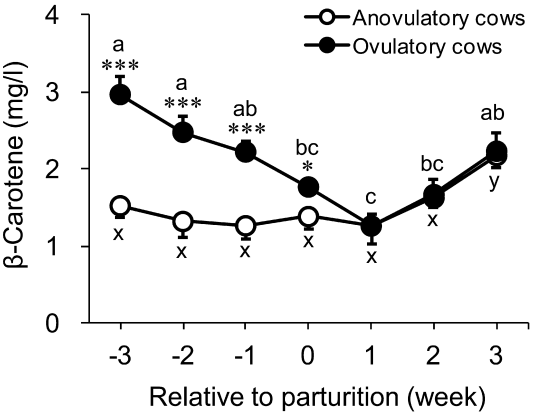

Fig. 5. The concentrations of β-carotene in plasma from 3 weeks prepartum to 3 weeks postpartum in ovulatory cows (n = 13) or anovulatory cows (n = 9) during the first follicular wave postpartum (mean ± SEM; solid, ovulatory cows; open, anovulatory cows). The first sampling week after parturition was regarded as week 0. There was an interaction between group and time ($P<0.0001$). *** indicates differences of $P<0.001$ and * indicates differences of $P<0.05$ between ovulatory and anovulatory cows. a, b, and c indicate differences of $P<0.05$ among ovulatory cows. x and y indicate differences of $P<0.05$ among anovulatory cows. Modified from Kawashima *et al.* (2009) [72].

cows during the first follicular wave postpartum: (1) higher energy status (lower GH and NEFA and higher IGF-1) during the prepartum period, (2) higher β-carotene during the prepartum period, and (3) lower proportional increases in milk yield during early lactation (Fig. 6). Furthermore, IGF-1 is an important factor in the development of the dominant follicle during the first follicular wave postpartum and subsequent increased insulin level and E2 peak, which ensure follicle maturation and ovulation (Fig. 6). Therefore, IGF-1 and insulin represent "metabolic signals" of the resumption of ovarian function postpartum in dairy cows. Moreover, β-carotene supply during the close-up dry period is effective in induction of ovulation during the first follicular wave postpartum in dairy cows. Thus, β-carotene is also one of the important nutritional factors for the resumption of postpartum ovarian function in dairy cows.

Because feed type and quality differ according to herd and season, feeding regimes for improvement of reproductive performance in high-producing dairy cows cannot be generalized. Therefore, the first step is to understand the nutritional status in the peripartum dairy cow, then compile suitable management strategies according to feed circumstances in each herd.

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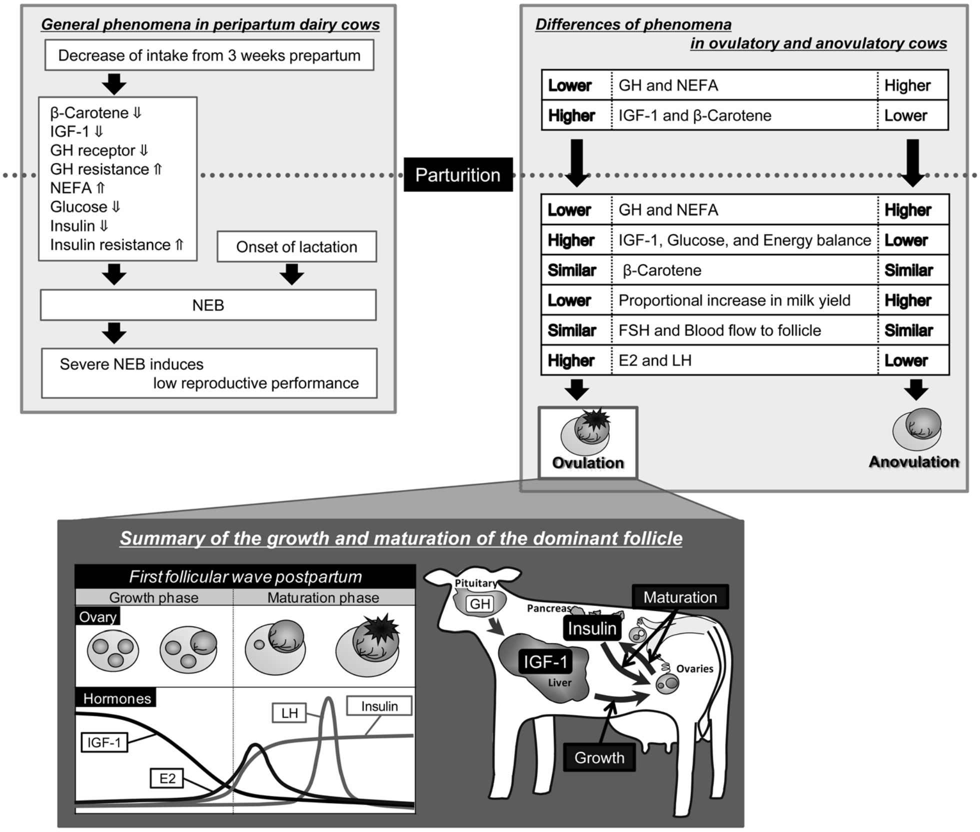

Fig. 6. Schematic representation of the nutritional status during peripartum and lactation and reproductive function during early postpartum in ovulatory and anovulatory cows at the first follicular wave postpartum. Ovulatory cows show higher energy status and β-carotene concentration during the prepartum period and lower proportional increases in milk yield during early lactation compared with anovulatory cows. In addition, higher IGF-1 levels stimulate follicular cell functions affecting growth of the dominant follicle during the first follicular wave postpartum, after which the levels decrease because of NEB. Subsequently, more E2 is secreted, and the E2 peak together with increased insulin enhances the maturation of the dominant follicle. Subsequently, E2 enhanced by IGF-1 induces an LH surge and the dominant follicle reaches ovulation. Modified from Kawashima *et al.* (2007) [17].

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