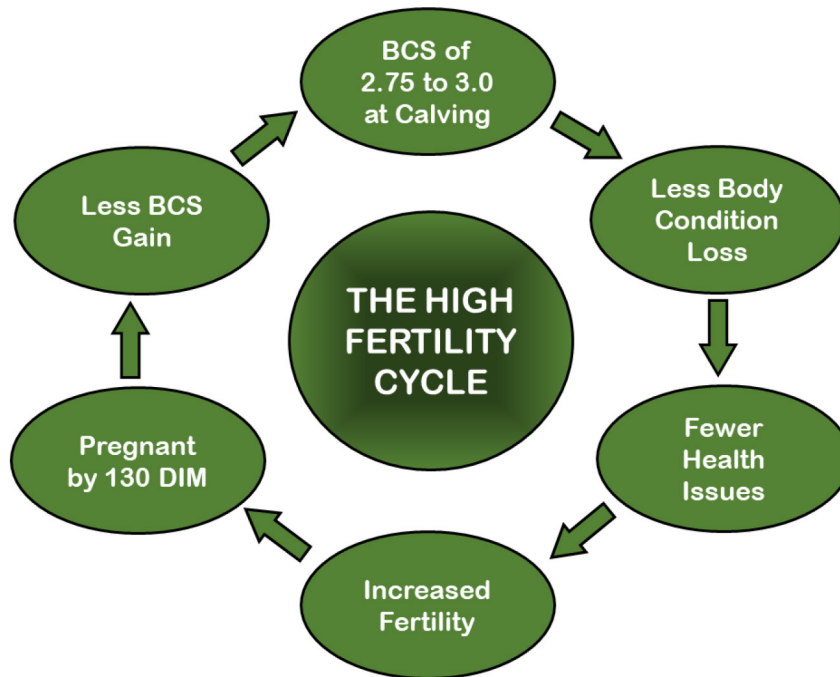


# The high fertility cycle

P. M. Fricke,<sup>1\*</sup> M. C. Wiltbank,<sup>1</sup> and J. R. Pursley<sup>2</sup>

## Graphical Abstract

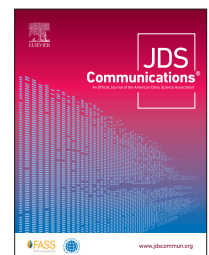


## Summary

The high fertility cycle describes the relationship between body condition score (BCS) change during the periparturient period and health events and reproduction in which lactating dairy cows that establish pregnancy by 130 days in milk have less BCS gain during the current lactation, undergo less BCS loss after calving, experience fewer health issues, have greater fertility at first insemination, and have reduced early pregnancy losses after establishment of pregnancy. And thus, the cycle continues. This minireview overviews these relationships and highlights the key concepts underlying the high fertility cycle in lactating dairy cows.

## Highlights

- Cows that establish timely pregnancies after the end of the voluntary waiting period have less BCS gain during the current lactation and undergo less BCS loss after the subsequent calving.
- These cows experience fewer health issues, have greater fertility at first insemination, and have reduced early pregnancy losses after establishment of pregnancy.
- The high fertility cycle offers a new paradigm that may explain much of the variation in reproductive performance among herds.



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# The high fertility cycle

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**Abstract:** The development of fertility programs and their adoption by the dairy industry over the past decade is a major driving factor underlying the dramatic increase in reproductive performance in lactating dairy cows during the past 20 years. Another major driving factor underlying this increase in reproductive performance is what we describe in this minireview as the “high fertility cycle.” We now know that reproductive performance and the incidence of certain periparturient health events are interrelated. The high fertility cycle describes the relationship between body condition score (BCS) change during the periparturient period and postpartum health events and subsequent reproductive performance in which lactating dairy cows that establish pregnancy by 130 d in milk have shorter calving intervals and thereby gain less BCS during the current lactation and dry off and calve at a lower BCS (2.75 to 3.0) than cows with a longer lactation. After calving, these cows undergo less BCS loss, experience fewer health issues, have greater fertility at first insemination, and have reduced early pregnancy losses after establishment of pregnancy and thereby become pregnant before 130 d in milk. This minireview overviews these relationships and highlights the key concepts underlying the high fertility cycle. Future randomized, controlled experiments are needed to causally link these relationships between BCS change and fertility in lactating dairy cows.

Over the past 2 decades, a revolution has occurred in the dairy industry regarding the reproductive performance of lactating cows. Whereas days open increased steadily from 1955 to 2000, days open from 2000 to 2010 dramatically decreased without a concurrent increase in the genetic trend for daughter pregnancy rate (Fricke and Wiltbank, 2022). The development of fertility programs and their adoption by the dairy industry over the past decade is a major driving factor underlying this reproduction revolution (Carvalho et al., 2018; Fricke and Wiltbank, 2022). Fertility programs, such as Double-Ovsynch and G6G protocols for first timed AI not only increase the AI service rate, but also increase pregnancies per AI (P/AI) beyond that achieved based on AI to a detected estrus (Fricke and Wiltbank, 2022).

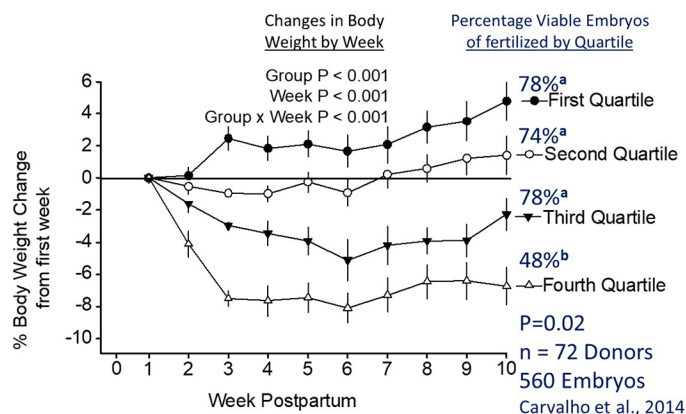
A second major driving factor underlying the reproduction revolution is what we describe in this minireview as the “high fertility cycle.” We now know that reproductive performance and the incidence of certain health events are interrelated. Several recent experiments have established a relationship between reproductive performance and the incidence of certain periparturient health issues linking increased reproductive performance with fewer health issues (Ribeiro et al., 2016; Barletta et al., 2017). Assessment of BCS has long been used as a practical management tool to assess body fat stores in Holstein dairy cows (Ferguson et al., 1994). Changes in BCS during the periparturient period are associated with profound effects on P/AI after submission of cows to fertility programs as well as pregnancy losses (Hernandez et al., 2012; Chebel et al., 2018; Middleton et al., 2019). This minireview overviews these relationships and highlights the key concepts underlying the high fertility cycle.

In 1992, Jack Britt sorted 76 lactating Holstein cows based on whether they lost ( $n = 30$ ) or maintained ( $n = 46$ ) BCS during the first 3 wk after calving (Britt, 1992). Body condition scores were recorded for 10 consecutive weeks after calving for these 2 groups of cows. Overall, BCS change during the first 5 wk postpartum

was  $-0.58$  for cows that lost and  $+0.06$  for cows that maintained BCS, whereas BCS change from wk 5 to 10 was  $+0.17$  for cows that lost versus  $-0.02$  for cows that maintained. Importantly, cows that lost BCS after calving had a greater BCS at calving than cows that maintained BCS after calving. Cows that maintained BCS after calving had more P/AI at first service (62% vs. 25%) and more P/AI across all services (61% vs. 42%) than cows that lost BCS after calving. Interestingly, milk yield during the first 70 d of lactation as well as mean 305-d lactation milk yield did not differ between cows that lost or maintained BCS after calving. Britt (1992) speculated that developing follicles or other reproductive tissues in high producing cows that experience severe BCS loss during the first 3 wk after calving are subjected to adverse metabolic conditions that compromise fertility at first insemination later during early lactation (Britt, 1992). This physiologic explanation for the effect of BCS loss on poor fertility has been termed the “Britt hypothesis.” Unfortunately, this hypothesis is difficult to test empirically, and this idea languished for many years. Recent data from several laboratories now support these observations regarding the relationship between BCS change and reproductive performance in lactating dairy cows.

The relationship between weight change after calving and embryo quality was evaluated in an experiment in which lactating Holstein cows ( $n = 71$ ; 27 primiparous and 44 multiparous) were weighed weekly from calving until 10 wk postpartum (Carvalho et al., 2014). Cows were divided into quartiles based on percent BW change from the first week after calving. The quartile analysis segregated cows based on those that gained weight (first quartile), maintained weight (second quartile), slightly lost weight (third quartile), and dramatically lost weight (fourth quartile) postcalving, and most of the BW change occurred during the first 3 wk postpartum (Figure 1). Cows in the fourth quartile that dramatically lost weight had increased NEFA concentrations during the first 3 wk after calving, whereas NEFA concentrations did not differ at

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**Figure 1.** Quartile analysis of percentage BW change from the first week postpartum in Holstein dairy cows. Data are shown as mean  $\pm$  SEM. <sup>a,b</sup>Different superscripts differ ( $P = 0.02$ ) as noted in the figure. Adapted from Carvalho et al. (2014).

10 wk postpartum when superovulation and embryo flushing was performed (Carvalho et al., 2014). In support of these data, high serum NEFA concentrations during the periparturient period have been associated with poor reproductive performance, increased incidence of diseases, and decreased milk production (Ospina et al., 2010a,b).

To assess embryo quality, cows were submitted to a superovulation protocol using a modified Double-Ovsynch protocol (Carvalho et al., 2014). All cows were inseminated and flushed, and cows were inseminated twice at 12 and 24 h after GnRH treatment. Seven days after GnRH treatment, ova or embryos were recovered using a nonsurgical shallow uterine horn flushing technique. Although the number of structures collected (ova or embryos) and the fertilization percentage were not affected by BW loss, other important embryo characteristics differed among BW quartiles (Figure 1). Thus, cows that experience extreme weight loss during the first 3 wk postpartum had poorer embryo characteristics including fewer quality 1 and 2 embryos, more degenerate embryos as a percentage of fertilized embryos, and fewer grade 1 and 2 embryos as a percentage of fertilized embryos than cows in the other 3 quartiles (Figure 1). Thus, cows that experience extreme weight loss during the first 3 wk postpartum have elevated NEFA concentrations and more poor-quality embryos compared with cows that gain, maintain, or slightly lose weight postpartum.

A recent study evaluated oocytes and serum lipids collected 20 h post-LH surge after the final GnRH treatment of a Double-Ovsynch protocol in 20 multiparous Holstein cows that were analyzed based on cows that maintained or gained versus cows that lost BCS during the first month of lactation (Ruebel et al., 2022). A total of 38 differentially expressed genes were identified; 4 of these genes were upregulated, whereas 34 were downregulated in cows that lost BCS during the first month of lactation. In addition, NEFA concentrations remained elevated 2-fold at 75 to 81 DIM in cows that lost versus cows that maintained or gained BCS during early lactation. Another recent study (Marei et al., 2022) reported differences in granulosa cell gene expression for cows that lose weight and experience severe negative energy balance postpartum. In agreement with the Britt hypothesis, the metabolic and oxidative

stress in dairy cows early postpartum can have long-term effects on granulosa cell function in preovulatory follicles at the time of insemination. The authors concluded that the interplay between the effects of antioxidants and NEFA might be useful to develop intervention strategies to minimize the effect of severe NEB on fertility.

Taken together, one possible physiologic mechanism by which change in BCS postcalving affects fertility in lactating dairy cows is through compromised oocyte or embryo quality, or both.

Carvalho et al. (2014) conducted a retrospective analysis of the effect of postpartum BCS change and reproductive performance in which 1,887 Holstein cows from 2 commercial dairy farms in Wisconsin were submitted to a Double-Ovsynch protocol for first timed AI, and BCS was evaluated at calving and 21 d after calving (Table 1). Overall, 42% of cows lost BCS, 36% of cows maintained BCS, and 22% of cows gained BCS during the first 3 wk of lactation. Similar to the results reported by Britt (1992), ECM did not differ among cows based on BCS change. Overall, P/AI 40 d after timed AI was only 25% for cows that lost BCS, 38% for cows that maintained BCS, and 84% for cows that gained BCS during the first 3 wk after calving. In addition, there was a location effect in which most of the cows that gained BCS and most of the dramatic change in P/AI due to BCS change predominantly occurred on only one of the 2 farms (Carvalho et al., 2014). In agreement with these results, Holstein cows with low BCS near the time of first AI as determined by an automated camera system and more pronounced decreases in BCS occurring close to the time of first AI were associated in lower odds of pregnancy (Pinedo et al., 2022). Pryce et al. (2001) evaluated BCS from calving until 26 wk of lactation and reported that cows that lost condition, those that were thinner than average at wk 10 of lactation, and those that were thinner on average over the first 10 wk had poorer reproductive performance.

Taken together, cows that undergo BCS loss during early lactation have decreased reproductive performance compared with cows that maintain or gain BCS after calving. The key question is, what factors are associated with cows that gain BCS after calving? A study by Barletta et al. (2017) answers this question.

Barletta et al. (2017) evaluated BCS change in 233 Holstein cows from 3 wk before the expected date of calving until 3 wk after calving. Similar to the experiment by Carvalho et al. (2014), P/AI 30 d after AI for cows submitted to first timed AI was dramatically associated with BCS change during the periparturient period and was 18% for cows that lost BCS (28% of cows), 27% for cows that maintained BCS (23% of cows), and 53% for cows that gained BCS (49% of cows). In agreement with other studies (Britt, 1992; Carvalho et al., 2014), mean milk production during the first 3 wk of lactation did not differ among cows based on BCS change during the periparturient period.

The incidence of periparturient health events is associated with decreased reproductive performance (Santos and Ribeiro, 2014). In addition to increased fertility, Barletta et al. (2017) reported that cows that gained BCS during the periparturient period also had fewer recorded health events including metritis, mastitis, ketosis, and pneumonia. Less than 40% of cows that gained or maintained BCS during the periparturient period had more than one of these health events, whereas more than 60% of cows that lost BCS during the periparturient period experienced one or more of these health events (Barletta et al., 2017).

**Table 1.** Effect of BCS change on pregnancies/AI (P/AI) for cows on farm 1 and 2 classified as losing, maintaining, or gaining BCS from parturition to 3 wk postpartum<sup>1</sup>

Item	BCS <sup>2</sup> change		
	Lost	Maintained	Gained
Cows, % (n)	41.8 (789/1,887)	35.8 (675/1,887)	22.4 (423/1,887)
P/AI at 40 d, % (n/n)	25.1 (198/789) <sup>c</sup>	38.2 (258/675) <sup>b</sup>	83.5 (353/423) <sup>a</sup>
P/AI at 70 d, % (n/n)	22.8 (180/789) <sup>c</sup>	36.0 (243/675) <sup>b</sup>	78.3 (331/423) <sup>a</sup>
Pregnancy loss, % (n/n)	9.1 (18/198)	5.8 (15/258)	6.2 (22/353)
BCS at parturition, mean ± SEM	2.93 ± 0.01 <sup>a</sup>	2.89 ± 0.02 <sup>b</sup>	2.85 ± 0.02 <sup>b</sup>
BCS at 21 DIM, mean ± SEM	2.64 ± 0.01 <sup>c</sup>	2.89 ± 0.02 <sup>b</sup>	3.10 ± 0.02 <sup>a</sup>
ECM <sup>3</sup> (kg/d; mean ± SEM)	30.9 ± 0.4	31.5 ± 0.4	28.7 ± 0.4

<sup>a-c</sup>Items with different superscripts within the same row differ ( $P < 0.05$ ).

<sup>1</sup>Adapted from Carvalho et al. (2014).

<sup>2</sup>Body condition score was evaluated at calving and at 21 DIM based on a 5-point scale.

<sup>3</sup>Mean ECM from calving to 21 DIM.

In agreement with these results, Chebel et al. (2018) reported that loss of BCS during the dry period was associated with greater incidence of uterine disease and indigestion; greater likelihood of treatment with antimicrobials, anti-inflammatories, and supportive therapy; and reduced likelihood of pregnancy after the first and second postpartum inseminations. Gobikrushanth et al. (2019) reported that cows that lost more than 0.75 BCS units from 2.3 d before calving until 34.6 d after calving had reduced fertility compared with other BCS change categories, including a smaller proportion of cows with a corpus luteum by 35 DIM, reduced pregnancy to first AI and pregnancy by 150 DIM, and reduced hazard ratio of pregnancy risk up to 250 DIM. Manríquez et al. (2021) evaluated the effect of BCS change during the first month after calving and reported that BCS change affected health and survival of Holstein cows. Although the relationship between BCS change during the periparturient period and the incidence of health events after calving based on these studies are only associative, future research should be aimed at improving reproduction for cows that experience health events during the transition period.

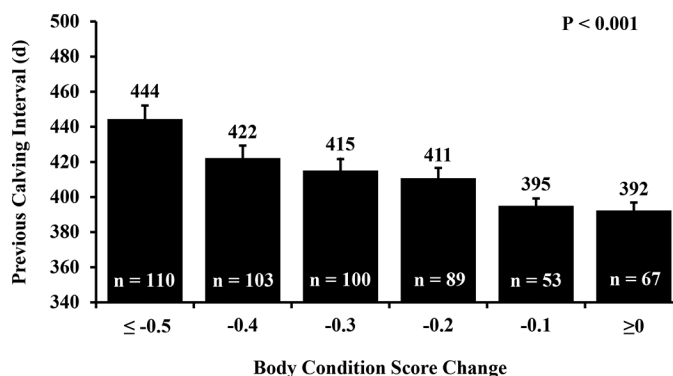
Regarding the question about factors associated with cows that gain BCS after calving, Barletta et al. (2017) reported that the primary factor associated with BCS change during the periparturient period was BCS 3 wk before expected calving. Only 34% of cows with BCS less than 3.0 lost BCS, whereas 51% of cows with BCS = 3.0 lost BCS and 92% of cows with BCS >3.0 lost BCS during the periparturient period. Cows that fail to establish pregnancy early after the voluntary waiting period spend more time in late lactation at a lower milk production level and tend to gain excessive BCS. Indeed, avoiding over-conditioned dry cows that experience excessive fat mobilization during the transition period may decrease metabolic issues including hyperketonemia (Rathbun et al., 2017).

So, how can we ensure that more cows gain BCS after calving? Nearly all cows in the study by Barletta et al. (2017) that gained BCS during the transition period had a BCS less than 3.0 at 3 wk before calving. Thus, calving cows at a lower BCS was associated with less BCS loss, greater fertility, and fewer health issues including metabolic problems. Based on data presented thus far, the next question is, how can we avoid calving cows with a high BCS? A recent study by Middleton et al. (2019) provides an answer to this question.

Middleton et al. (2019) evaluated BCS change within 1 wk of calving until 30 d after calving in 851 Holstein cows on a commer-

cial dairy farm in Michigan. This study linked the calving intervals of the previous lactation to BCS change of cows after calving. Calving interval is determined by the fixed intervals of gestation length and the voluntary waiting period and the highly variable interval of calving to conception, which reflects reproductive efficiency on a dairy farm. Thus, cows with longer calving intervals during the previous lactation became pregnant later than cows with shorter calving intervals. Middleton et al. (2019) reported that cows with longer calving intervals in the previous lactation had greater BCS at calving and lost more BCS during the first 30 d after calving (Figure 2).

In agreement with other studies (Carvalho et al., 2014; Barletta et al., 2017), cows that maintained or gained BCS after calving had more P/AI, less pregnancy loss, and fewer health events than cows that lost BCS after calving (Middleton et al., 2019). Differences in P/AI and pregnancy losses in favor of cows that maintained or gained BCS during the first 30 DIM were maintained even when cows with health events were removed from the analysis. An excellent summary of the results from the study by Middleton et al. (2019) is captured by the title of their paper, “The high fertility cycle: How timely pregnancies in one lactation may lead to less



**Figure 2.** Relationship between average previous calving interval (d) and BCS change evaluated ≤1 wk before parturition and 27 to 33 d postpartum in multiparous lactating Holstein dairy cows. Data are shown as mean ± SEM. Adapted from Middleton et al. (2019).



body condition loss, fewer health issues, greater fertility, and reduced early pregnancy losses in the next lactation.”

The high fertility cycle offers a management paradigm that can be easily implemented and monitored on commercial dairy farms. The best way to get a herd into the high fertility cycle is to implement a reproductive management strategy to maximize the proportion of cows in the herd that are pregnant by 130 DIM (Middleton et al., 2019). Many studies have concluded that body condition scoring may be an effective management strategy to optimize health and fertility of lactating dairy cows (Carvalho et al., 2014; Gobikrushanth et al., 2019; Manríquez et al., 2021). Future studies to assess management strategies for feeding cows during lactation (Boerman et al., 2015) or the dry period (or both) (Beever, 2006; Daros et al., 2021) to manage BCS and for differentially grouping cows based on BCS targets are needed to determine how to better manage BCS throughout lactation. Although BCS scoring is easily performed by properly trained personnel on dairy farms, emerging technologies involving 3-dimensional imaging systems (Xavier et al., 2022) and digital camera imaging systems (Mullins et al., 2019) may soon automate this task and provide a more frequent and uniform measure of BCS in dairy cows. Future randomized, controlled experiments are needed to causally link these relationships between BCS change and fertility and health events in lactating dairy cows.

Based on the collective results from the studies in this mini-review, we can now clearly define a relationship in which herds that manage to get their cows pregnant rapidly after the end of the voluntary waiting period are likely to calve cows at a lower BCS and that this, in turn, leads to more cows maintaining or gaining BCS after calving. Cows that maintain or gain BCS after calving have greater fertility than cows that lose BCS. The high fertility cycle coupled with the dramatic increases in reproductive performance due to the development and adoption of fertility programs offer a new paradigm that may explain much of the variation in reproductive performance among herds. The best strategy to avoid over-conditioned cows at parturition is to implement a reproductive management strategy to maximize the proportion of cows in the herd that are pregnant by 130 DIM (Middleton et al., 2019). The goal of every farm should be to strive to get their herd into the high fertility cycle and keep it there. The following are key considerations to achieve this: (1) implement BCS monitoring for transition cows 3 wk before calving, at calving, 3 wk after calving, and at AI; (2) use fertility programs to help establish pregnancy quickly after the end of the voluntary waiting period; (3) set a cut-off for the number of times individual cows will be inseminated; and (4) consider nutritional strategies to prevent late-lactation cows from gaining too much body condition. Future randomized, controlled experiments are needed to causally link these relationships between BCS change and fertility in lactating dairy cows.

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## Notes

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