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# EFFECT OF POSTPARTUM ENDOCRINE FUNCTION, METABOLISM, AND MASTITIS ON FERTILITY IN HIGH-YIELDING COWS – A REVIEW*

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**Abstract**

**Decreasing fertility in dairy cows, especially in the highest yielders, may be due to excessive metabolic burdens placed on their bodies. Many authors attribute decreasing reproductive efficiency in high-yielding cows to energy deficiencies in early lactation and to associated metabolic and hormonal disorders. The complexity of the issues involved in the efficient reproductive management of cows and the scientifically and practically important understanding of factors affecting fertility in high-producing cows mandate continuous updating of existing knowledge. The aim of this study was to present the effect of postpartum endocrine function, metabolism, and mastitis on fertility in high-yielding cows. Gaining insight into these mechanisms and their relationships with factors such as nutrition and milk yield appears to be crucial for improving dairy cow fertility.**

**Key words: hormones, ovarian function, postpartum endocrine function, postpartum metabolism**

Since the 1970s, the strategy for using and improving Holstein-Friesian cattle has focused on maximising milk yield. Unfortunately, for more than 20 years this has been associated with many adverse consequences, such as a decline in reproductive efficiency (Lavon et al., 2011 a; Green et al., 2012; Grimard et al., 2013; Piccardi et al., 2013; Pritchard et al., 2013; Keskin et al., 2016) and a higher incidence of metabolic disorders (Mordak, 2008). A reduction in length of productive life has also been observed (Mordak, 2008; Ahlman et al., 2011; Cardoso et al., 2013; Rzewuska and Strabel, 2014; Adamczyk et al., 2017). Especially in recent years, a clear trend has been visible according to which the proportion of cows culled due to reproductive abnormalities and mastitis is increasing (from 30% in 1997–2007 to 55.1% in 2012), while fewer cows are removed from the herd due to low milk yield (Adamczyk et al., 2017). The directional selection for high milk yield results in an increased inter-

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val between parturition and first oestrus, an increased postpartum interval, weaker external signs of oestrus (silent oestrus), ovulation abnormalities, impaired ovarian luteal function, a poorer conception rate, longer oestrus cycles, enlargement of the uterus and cervix, and deterioration in oocyte quality (Jaśkowski et al., 2006). As well, *in vitro* studies have shown that oocytes from cows with high genetic merit for milk yield do not develop as well as those from cows of medium genetic potential (Jaśkowski et al., 2006; Leroy et al., 2008; Remnant et al., 2015).

**Postpartum endocrine and ovarian function in cows in relation to fertility**

Impaired fertility in modern dairy cows often appears to be due to a nutrient deficit, mainly during the transition period (Jaśkowski et al., 2006). The period from three weeks before calving to three weeks after calving is considered critical in the life of a cow. Two weeks prior to parturition, the amount of feed ingested decreases (Thatcher et al., 2010; Bisinotto et al., 2013), progesterone concentration significantly decreases, and estradiol level increases (Thatcher et al., 2010). After calving, increases in dry matter intake (Bisinotto et al., 2012) and milk yield are paralleled by greater intensity of metabolic processes and blood flow through the liver, where the above-mentioned hormones are broken down (Green et al., 2012; Piccardi et al., 2013; Żukowski, 2013; Ferrareto et al., 2014). The increased degradation of steroid hormones may have a significant negative effect on the development of oocytes and subsequent embryonic development and the progression and intensity of signs of oestrus, and thus on cows' reproductive efficiency (Bisinotto et al., 2012; Ferrareto et al., 2014). The observed hormonal changes, combined with periparturient stress, environmental factors, and herd management, may lead to a negative energy balance, which reaches its nadir 2–3 weeks after calving; with advancing lactation, the energy balance becomes positive. An energy balance of zero is generally restored after approximately 8–10 weeks of lactation (Thatcher et al., 2010). Negative energy balance is regarded as one of the factors modulating the hypothalamic-pituitary-ovarian (Bisinotto et al., 2012) and somatotropic axes (Thatcher et al., 2010). Considerable energy deficiency may adversely affect the secretion of pituitary gonadotropin-releasing hormone (GnRH), which in mammals is crucial for reproductive function (Żukowski, 2013; Lucy et al., 2014) and may uncouple growth hormone (GH) secretion from that of insulin-like growth factor 1 (IGF-1) in the liver (Thatcher et al., 2010). The change in insulin concentration in the postpartum period also has a negative effect on the development of ovarian follicles. In fact, IGF-1 and insulin have a direct effect on ovaries, making them more sensitive to the effects of luteinising hormone (LH) and follicle-stimulating hormone (FSH) (Crowe et al., 2004; Leroy et al., 2008; Thatcher et al., 2010; Bisinotto et al., 2012; Dova et al., 2013; Ferrareto et al., 2014). Another key hormone for reproduction in cows is progesterone, which is essential for the initiation of pregnancy, ovulation of healthy oocytes, maintenance of uterine quiescence, nourishment, survival of the embryo and subsequently of the foetus, and normal parturition. Progesterone also plays a significant role in regulating luteal regression in non-pregnant cows, preparing the uterus for pregnancy, and influencing the development of oocytes. Decreased progesterone concentration increases the contents of other hormones (e.g. PGF2α, estradiol, LH), a process which may cause embryonic death. Progesterone concentration can be influenced by feed intake, milk yield, or other factors, such as the external administration of various substances which can affect its metabolism and excretion from the body (Inskeep, 2004; Brown et al., 2012; Monteiro et al., 2014; Wiltbank et al. 2014; Zwyrzkowska and Kupczyński, 2014; Stratman et al., 2016). It is thought that suboptimal concentration of this hormone in the bloodstream influences endometrium morphology, leading to changes in secretory function of this organ during early pregnancy and enhancing prostaglandin $F2_{\alpha}$ ($PGF2_{\alpha}$) synthesis in response to oxytocin. In addition, decreased progesterone concentration is paralleled by greater LH concentration, more rapid maturation of ovarian follicles, lower amounts of intrafollicular IGF-1, and poorer embryo quality. The significant effect of progesterone concentration on reproductive efficiency is clearly demonstrated by the results of studies showing a positive association between serum progesterone concentration and first insemination success (Bisinotto et al., 2013). Increased blood flow and hepatic catabolism of steroids are considered to be among the reasons for reduced progesterone concentration in high-yielding cows compared to lower-yielding cows or non-lactating cows (Yusuf et al., 2011; Bisinotto et al., 2013; Wiltbank et al., 2014).

Fertility in dairy cows is also influenced by thyroid hormones (which, at elevated levels, have a positive effect on the date of first postpartum oestrus, the length of calving intervals, and conception rate). By influencing IGF-1 levels, they regulate protein synthesis and the proliferation of granulosa cells (Jaśkowski et al., 2006). The level of IGF-1 has been shown to regulate the effect of LH and FSH on steroidogenesis, modulating the hypothalamic-pituitary-ovarian axis function and determining the growth and maturation of oocytes and the formation of embryos (Leroy et al., 2008; Grimard et al., 2013; Drackley and Cardoso, 2014). The level of IGF-1 has also been found to affect the oviduct and uterine environments (Grimard et al., 2013). In high-yielding cows, the blood concentration of the above-mentioned substances is reduced, especially within 1–2 weeks of calving (Jaśkowski et al., 2006; Grimard et al., 2013).

The first wave of follicular growth in a Holstein-Friesian cow, depending on the animal's energy balance, takes place within 5–7 days of calving and results from an elevated concentration of FSH in the bloodstream (Thatcher et al., 2010). However, because considerable amounts of progesterone are produced during that time in connection with the progesterone-dominant luteal phase, which limits secretion of LH, the dominant ovarian follicle cannot ovulate. This results in two to four (normally three) waves of follicular growth during the oestrus cycle. The number of waves, which depends to a certain extent on the way animals are fed, is repeatable within individual cows, although it may differ between animals in a herd (Crowe et al., 2004; Inskeep, 2004). Research also shows that more favourable reproductive results are to be expected for cycles comprising two rather than three waves of follicular growth (Remnant et al., 2015). About 40–50% of cows ovulate in the first postpartum cycle. The first postpartum ovulation is observed, on average, between the 27th and 30th days of lactation (Galvão et al., 2010; Brown et al., 2012). In about 30–40% of animals, the first oestrus cycle does not end in ovulation, which occurs in the next cycle. The remaining 10–30% of the cows ovulate only after 50 days (Galvão et al., 2010;

Thatcher et al., 2010). Better reproductive results are to be expected in cows that resume reproductive function in a shorter time after parturition (Galvão et al., 2010; Thatcher et al., 2010).

**Postpartum metabolism in cows in relation to fertility**

One factor predisposing high-yielding cows to reduced fertility is their ability to mobilise energy reserves, mainly from adipose tissue (Leroy et al., 2008; Roy et al., 2011; Bisinotto et al., 2012; Strucken et al., 2012), but in some cases from muscle tissue as well (Strucken et al., 2012; von Leesen et al., 2014), and to increase their utilisation of amino acids, minerals, and vitamins (Bisinotto et al., 2012) during the critical period of early lactation. Excessive emaciation may give rise to metabolic changes leading to functional changes in the reproductive system and impairment of fertility (Jaśkowski et al., 2006; Green et al., 2012), e.g. reduced conception rate or increased likelihood of pregnancy loss (Herlihy et al., 2013; Stratman et al., 2016). It is estimated that, despite the efforts of breeders, metabolic and infectious disease affect 45% to 60% of cows during the first months of lactation regardless of milk production level, breed, or herd management system (Bisinotto et al., 2012). Another reason for reproductive failure in dairy cows is weak oestrus symptoms. It has been reported that increased milk yield is accompanied by a greater incidence of silent oestrus. This is attributed to the body's natural response to avoid pregnancy under the stress of, for example, energy underfeeding in early lactation (Lopez et al., 2004; Dobson et al., 2007).

The negative impact of high milk yield on reproductive parameters is explained by the fact that the postpartum insemination period occurs at the peak of milk production. The negative energy balance during this period may affect not only endocrine function (as presented above) but also fat and carbohydrate metabolism in early lactation. Decreased blood glucose concentration has an adverse influence on reproductive function. Glucose plays a critical role in oocyte maturation and blastocyst and foetal development, and is also essential for the release of oocytes from mature follicles (Bisinotto et al., 2012; Lucy et al., 2014; Stratman et al., 2016). Other authors attribute reproductive failure to the fact that a low blood glucose level is associated with a high level of free unsaturated fatty acids, which, as a result of several biochemical processes, are converted into ketone compounds (β-hydroxybutyric acid, acetate, acetone) (Lucy et al., 2014). High contents of non-esterified fatty acids and β-hydroxybutyric acid are closely associated with the risk of such abnormalities as uterine disorders (clinical metritis and subclinical endometritis) (Galvão et al., 2010), displacement of the abomasum, placental retention, ketosis, and liver diseases. They have also been implicated in reduced milk yield and diminished first insemination success, and thus, in turn, in the culling of cows from the herd (Chamberlin et al., 2013; Drackley and Cardoso, 2014).

Another consequence of the failure to meet the energy requirements of cows is a series of changes leading to impairment of the immune system (Mordak, 2009; Thatcher et al., 2010; Bisinotto et al., 2012). It was found that reduced dry matter intake and the accompanying negative energy balance and elevated concentration of ketone bodies predispose cows to more frequent reproductive disorders (metritis, endometritis) and to decreased reproductive efficiency (Thatcher et al., 2010; Cardoso et al., 2013). These disorders may, in turn, lead to ovarian cycle abnormalities, the formation of cysts, lengthening of the luteal phase (Mordak, 2008), and a longer period of uterine involution, which promotes uterine diseases (Bisinotto et al., 2012). Perinatal undernutrition also results in deficiency of vitamins, especially major antioxidants such as β-carotene, vitamin A (retinol), vitamin E (α-tocopherol) (Bisinotto et al., 2012), and macro- and microelements (hypocalcaemia, hypophosphatemia, hypomagnesemia). This deficiency has an effect on cows' health and reproduction (Leroy et al., 2008; Mordak, 2009). Periparturient hypocalcaemia may affect as many as 40–50% of cows, leading to diseases, such as mastitis, metritis, placental retention, and displaced abomasums, which negatively influence reproductive efficiency (Bisinotto et al., 2012; Chamberlin et al., 2013; Drackley and Cardoso, 2014). In cows that have experienced milk fever, the likelihood of conception is decreased 2.25-fold compared to unaffected animals (Chebel et al., 2004). Therefore, emphasis is placed on high-quality feed, especially before and after calving; when properly supplemented with probiotics and prebiotics, this may positively influence immune function, as a result of which improved reproductive performance is to be expected (Mordak, 2009; Bisinotto et al., 2012; Żukowski, 2013).

In practice, the problem of cows experiencing nutrient deficiency in early lactation is addressed by adding high-protein feeds to the diet (Skrzypek et al., 2005; Januś and Borkowska, 2006; Roy et al., 2011). Becausey these feeds normally contain too much protein in relation to the amount of energy that can be ingested by the cow, large amounts of ammonia are released from the ruminal degradation of protein (Skrzypek et al., 2005; Januś and Borkowska, 2006). It is estimated that 75–85% of excess protein is excreted from a cow's body in faeces (Guliński et al., 2015) and urine (Roy et al., 2011; Henao-Velásquez et al., 2014). In contrast to urine, the amount of protein excreted in faeces is stable and cannot be increased (Guliński et al., 2015). The insufficient amount of energy available to ruminal microorganisms as a result of excess protein increases urea levels in the body; this in turn has a negative effect, both directly and indirectly, on reproductive function. This negative impact affects the development of ovarian follicles (quantity, size), ovulation, the egg fertilisation process, and embryo development and implantation (Skrzypek et al., 2005; Januś and Borkowska, 2006; Roy et al., 2011). In *in vitro* conditions, urea was also found to adversely affect sperm survival (Skrzypek et al., 2005) and to impair the development of oocytes (Sinclair et al., 2014). Excess urea in the body exerts an indirect effect through decreasing uterine pH (Skrzypek et al., 2005; Bisinotto et al., 2012; Sinclair et al., 2014). Reduced pH increases the secretion of prostaglandins $E_2$ and $F_{2\alpha}$ by endometrial cells. The increase in $PGF_{2\alpha}$ content has been especially implicated in the connection between high urea levels and reproductive disorders. This results from the impairment by high urea levels of peri- and postparturient secretion of oestrogens and progesterone, which simultaneously disrupts the effects of these hormones on the uterus (Skrzypek et al., 2005; Roy et al., 2011). The risk of these abnormalities increases significantly when plasma urea levels exceed 190–200 mg/l (Skrzypek et al., 2005).

**Postparturient mastitis in cows in relation to fertility**

Increasing attention has recently been paid to udder inflammation in the context of its relationship with reproductive disorders (Skrzypek et al., 2007). The association between udder health and cow fertility is based on a close functional relationship, which leads to disruption of the endocrine and immune systems, resulting in oestrous cycle abnormalities, ovarian disorders, and early embryo death (Skrzypek et al., 2007; Roth et al., 2013; Isobe et al., 2014). These changes are dependent on the aetiological agent of mastitis and the time of its occurrence; their progression varies according to the form of inflammation (Hertl et al., 2010; Lavon et al., 2010, 2011 b; Roth et al., 2013; Asaf et al., 2014; Wolfenson et al., 2015). Mastitis is the cause of changes in the concentration or activity of cortisol, cytokines, prostaglandin F-2α, GnRH, luteinising hormone, follicle-stimulating hormone, progesterone, estradiol-17β, prolactin, immunoglobulins, and reactive oxygen metabolites (Skrzypek et al., 2007; Pinedo et al., 2009; Lavon et al., 2010, 2011 b; Furman et al., 2014; Wolfenson et al., 2015). Research has shown that during the follicular phase or in early oestrus, Gram-negative bacterial liposaccharides (endotoxins) have the effect of delaying the pre-ovulatory LH wave and ovulation in one-third of cows (Wolfenson et al., 2015). It has also been demonstrated that liposaccharides or cytokines reduce the production of steroid hormones (including estradiol) in ovarian theca and granulosa cells (Furman et al., 2014; Lavon et al., 2011 b; Wolfenson et al., 2015). Another negative consequence of mastitis comprises changes in uterine sensitivity to the action of prostaglandins F-2α and $E_2$ or oxytocin (Hertl et al., 2010; Rahman et al., 2012). A negative effect of the subclinical form of mastitis was also reported (Pinedo et al., 2009; Lavon et al., 2010; Rahman et al., 2012; Lomander et al., 2013), especially during flare-ups (Skrzypek et al., 2007). This situation is particularly prevalent during oestrus, when increased oestrogen concentration significantly reduces the number of macrophages and weakens granulocyte activity, thus inhibiting the ability of somatic cells to undergo phagocytosis (Skrzypek et al., 2007). Because of their duration, subclinical forms of mastitis may disturb long-term processes such as follicular growth and development even more strongly than the acute form of this disease (Lavon et al., 2011 b; Rahman et al., 2012; Roth et al., 2013). Chronic subclinical mastitis, like short-term acute inflammation, may delay ovulation in as much as 30% of cows (Lavon et al., 2010). Prolonged subclinical mastitis, which is characterised by a small (150,000 to 450,000) or moderate (450,000 to 1 million) increase in LCC, needs special attention, because the conception rate may be reduced to almost the same extent in both cases (Lavon et al., 2011 a).

Understanding the mechanisms described above and their relationships with factors such as nutrition and milk yield and gaining insight into the effect of environmental factors on endocrine function appear to be crucial for improving dairy cow fertility.

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