Ovarian Dysfunction in Dairy Cows

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Take Home Messages

- For this paper, lactating dairy cows that fail to ovulate by 40 to 60 days postpartum are defined as having ovulatory dysfunction. Delayed ovulation is associated with lower conception rates and longer open days. Incidence may range from 10% to 50% of cows across herds.
- Two main conditions are observed in cows with ovulatory dysfunction: recurrent follicular waves with anovulation of a dominant follicle or development of a follicular cyst.
- Metabolic, infectious, inflammatory and stress conditions may predispose to ovulatory dysfunction. Heritability estimated by Zwald et al. (2004) is 0.07 for first lactation animals to 0.05 across all lactations.
- Programmed hormonal breeding programs (OvSynch) can ensure timely insemination postpartum, but conception rate may be only 20% at first insemination. Intravaginal CIDR combined with OvSynch protocols may improve conception rate to timed artificial insemination in these cows.

Introduction

Reproductive efficiency is an important factor influencing profitable milk production. Reproductive efficiency is best measured by pregnancy rate (PR), the proportion of open cows which become pregnant every 21 days from the voluntary waiting period (VWP). Heat detection (insemination) rates and conception rates determine PR. Economic losses are 6x greater when PR is below 20% than when PR is above 20%. A reasonable herd goal is to achieve a PR of 25% or greater. With a PR of 25% or greater, 50 to 70% of cows in the herd will have calving intervals under 14 months, or days open less than 145 days. To achieve this, ovarian cycling needs to resume and uterine involution needs to be complete by 40 to 50 days postpartum, respectively. A major cause of reproductive inefficiency in dairy herds is ovulatory dysfunction, failure to ovulate by 40 days postpartum.

■ Definition Ovarian Dysfunction

Butler (2003) has described the reduction in fertility when cows fail to ovulate the first dominant follicle by 20 days postpartum, and first ovulation is delayed to 40 to 60 days postcalving. In this paper, ovarian dysfunction will be defined as a delay in first ovulation beyond 40 to 60 days postpartum in lactating dairy cows. The delay in ovulation may be associated with two dysfunctions: repeated follicular waves with failure to ovulate a dominant follicle ≥10 mm in size (Butler 2003; Chong et al., 2015; Peter et al. 2009; Wiltbank et al. 2002), or development of an ovarian follicular cyst (OFC), an ovarian structure > 25 mm in size that persists on the ovary for more than 10 days in the absence of a corpus luteum (CL) (Peter et al., 2004; Vanholder et al., 2006). A rare third condition may exist, anovulation with failure to develop a follicle ≥10 mm in size, commonly referred to as atretic ovaries (Peter et al., 2009, Wiltbank et al., 2002). This condition is associated with a genetic component or extreme malnutrition, and is not common in dairy herds and will not be discussed in this paper. Estrous cycles may also be inhibited from retention of a CL, but this condition is usually associated with uterine infection and will not be considered a component of ovarian dysfunction.

■ The Players

The reproductive axis consists of the hypothalamus, the anterior pituitary gland, the ovary and uterus. The hypothalamus is a region of the brain that coordinates many homeostatic processes by integrating neural, endocrine, and metabolic inputs. The hypothalamus releases pulses of gonadotropin hormone (GnRH), which regulates ovarian function through stimulating anterior pituitary release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Hormones from the anterior pituitary gland stimulate the emergence of follicular waves on the ovary (FSH) and stimulate growth, development and ovulation of a dominant ovarian follicle (LH). Ovarian follicular waves emerge every 7 to 8 days due to an increase in FSH. Follicular waves first appear as a cohort of 4 to 6 follicles 4 to 6 mm in diameter. When a follicle reaches 8.5 mm in size, it deviates from the follicular pool, producing estradiol and inhibin, and repressing the growth of other ovarian follicles. When greater than 10 mm in size, the follicle is dominant and potentially ovulatory if a surge in LH occurs. If there is no surge in LH, the follicle becomes atretic in 4 to 6 days, and a new follicular wave emerges associated with an increase in FSH.

When the follicle ovulates, a CL forms from the follicular theca and granulosa cells producing progesterone. If pregnancy is not established, the uterus produces prostaglandin F2 alpha (PGF2α) after 16 days, causing regression of the CL and initiating a new estrous cycle. A typical estrous cycle averages

21 days with a range of 18 to 24 days. During the estrous cycle, 2, 3 or 4 follicular waves may occur.

■ Normal Postpartum Function

After calving, a surge in FSH from the anterior pituitary gland occurs within the first week post-calving (Adams et al., 2008; Butler, 2003; Wiltbank et al., 2002). This stimulates the emergence of the first follicular wave, about 4 to 6 days post-calving. This wave is detectable as a pool of follicles greater than 4 mm on each ovary. Butler (2003) reports that by 6 to 8 days postpartum all cows develop at least one large follicle. When a follicle reaches 8.5 mm in size it deviates from the remaining follicles and develops dominance. Dominance is associated with the expression of LH receptors on granulosa cells and production of estradiol and inhibin. Inhibin causes other follicles to regress. Sensitivity to LH causes the dominant follicle to continue to grow and increase estradiol production. Increasing estradiol stimulates further production of LH from the pituitary gland, and LH further stimulates follicular growth in a positive feedback loop. Increasing estradiol production leads to a surge release of LH and ovulation of the dominant follicle, typically when about 17 mm in size (range 10 to 20 mm). If all occurs in a coordinated fashion with adequate hormonal concentrations, first ovulation should occur between 14 to 21 days postpartum. Metabolic hormones, particularly insulin and insulin-like growth factor 1 (IGF-1), influence follicular maturation and response to, and production of, the critical sex hormones to initiate ovulation.

Typically postpartum, serum concentrations of estradiol and progesterone decline rapidly from precalving concentrations. Progesterone concentration is less than 0.2 ng/ml and estradiol concentration is less than 2 pg/ml by 2 to 4 days postcalving. With the emergence of an ovulatory dominant follicle, serum estradiol concentrations increase above 2.0 pg/ml. With ovulation, serum progesterone concentrations will increase to greater than 1.0 ng/ml, indicating active luteal tissue on the ovary.

Beam and Butler (1997) observed the ovulation of the first dominant follicle in 45% of animals. If the first dominant follicle failed to ovulate, they observed two outcomes. In 35% of cows, the follicle regressed and subsequent follicular waves emerged on a frequency of about 8 days until ovulation occurred, which was on average 51 days postpartum. In the remaining 20% of cows, a large OFC developed, ≥25 mm in size, which was associated with a depression in follicular waves to a 19-day frequency, and delayed first ovulation until 48 days on average. Fertility was reduced and days to pregnancy was increased in cows that failed to ovulate the first dominant follicle postpartum.

■ Risk Factors for Delayed Ovulation

Butler (2003) identified negative energy balance, or metabolic stress, as a major risk factor for delayed ovulation. However, uterine infection, mastitis, and inflammation and stress in general may also impair the initiation of ovarian cycling. Cows typically experience negative energy balance during the first 8 weeks postpartum (range 4 to 12 weeks), with the greatest negative deficit occurring between 5 to 14 days postcalving. After 2 weeks postcalving, cows steadily increase in energy balance and go into positive energy balance by, on average, 8 weeks postcalving. Dominant follicles (≥10 mm) that emerge after energy balance nadir postpartum are more likely to ovulate than dominant follicles that emerge before the energy balance nadir postpartum (Butler 2003; Chong, 2015).

Dominant follicles that fail to ovulate have lower production of estradiol and fewer LH receptors, and tend to grow more slowly than follicles that ovulate. This is associated with reduced LH pulse frequency and lower mean serum concentration of LH and estradiol. Failure to ovulate the first dominant follicle is associated with lower serum insulin and IGF-1, higher serum nonesterified fatty acids, lower body condition score and greater body condition loss (Ambrose et al., 204; Beam and Butler, 1997, 1999; Butler, 2003; Butler et al., 2004; Chong et al., 2015, Vanholder et al., 2005). Pituitary release of LH is diminished and ovarian sensitivity to LH stimulation of steroidogenesis is diminished.

■ Incidence of Ovulatory Dysfunction

The incidence of ovulatory dysfunction is quite variable across herds and depends on the number of days in milk that defines anovulation, but reports range from 28 to 54.1% for primiparous cows and 15 to 31.5% for multiparous cows from 49 to 71 days in milk. Beam and Butler (1997, 1999), Butler (2003) and Chong et al. (2015) suggest about 40 to 45% of cows ovulate the first dominant follicle postpartum, 35% undergo successive follicular waves before first ovulation, and about 20% of cows develop an OFC. Garverick (1997) reported anovulatory failure occurred in 10 to 13.5% of cows due to development of an OFC. Zwald et al. (2004), using herd records collected through on farm data systems, reported that lactational incidence rates of OFC ranged from 3 to 39% across 340 herds, with a mean lactation incidence rate of 8%. In one study, Roth et al. (2012) observed an incidence of 10.3% anovulatory cows, whereas in a second study, they observed 36% of postpartum cows as anovulatory due to repeated regression of dominant follicles or development of OFC.

■ Etiology

Causes of ovulatory failure with repetitive follicular waves seem to be related to low LH secretion from the pituitary due to dampened pulse generation from the hypothalamus and reduced responsiveness to LH in granulosa cells in the follicle. Dominant follicles form, but fail to produce adequate estradiol to effect a surge in LH to cause ovulation. In the majority of cases, dominant follicles develop, but steroidogenic capacity is limited. The GnRH pulse generator in the hypothalamus is reduced, reducing LH pulse frequency and amplitude. However, granulosa cells in the dominant follicle have fewer LH receptors and a reduced production of estradiol, which appears associated with reduced insulin and IGF-1. Insulin infusion early postpartum increases estradiol secretion independently of changes in LH pulse frequency (Butler et al., 2004) suggesting insulin concentrations in follicular fluid influence aromatase activity and steroidogenesis. Metabolic signals associated with nutritional stress seem to dampen the hypothalamic pulse generator for LH but not FSH, reducing ovarian follicular stimulation of the dominant follicle but not diminishing follicular waves. The dominant follicle is less responsive to LH inputs. Ovulation is delayed due to dampening of the hypothalamic-ovarian axis.

It is less clear why some cows form OFC, which result from continued growth of the dominant follicle rather than regression. It seems to be an imbalance between apoptosis and growth (Halter et al., 2003; Peter, 2004; Silva et al., 2002; Vanholder et al., 2005). As with anovulatory dominant follicles, cows that develop OFC have lower insulin and IGF-1 in serum and in follicular fluid (Hein et al., 2005; Rodriguez, 2011). The defect, as in anovulation of a dominant follicle, is in the hypothalamic-pituitary-ovarian axis, but in OFC, LH tends to have higher serum concentrations than observed with anovulatory follicles, estradiol production from the OFC may be quite high, and progesterone production may be between 0.2 to 1.0 ng/ml (Halter et al., 2003; Roth et al., 2012). Unlike anovulatory follicles that regress, OFC continue to grow past 20 mm, due to the LH stimulation, and continue to produce estradiol. However, despite very high concentrations of estradiol, the hypothalamus is unresponsive to the positive feedback of estradiol and fails to elicit an LH surge to cause ovulation. The defect is in the hypothalamic response to estradiol.

Responsiveness of the hypothalamus to estradiol to release LH requires progesterone in cows with OFC. Serum progesterone concentrations >2 ng/ml restore the responsiveness of the hypothalamus to estradiol. Progesterone treatment can result in an LH surge and ovulation (Halter et al., 2003). Vanholder (2006) reports that when OFC become non-steroidogenic, or if they develop luteal tissue producing progesterone, they will no longer interfere with cyclicity. A major difference between OFC and anovulatory

follicles is OFC depress follicular turnover to 19 days whereas anovulatory follicles are associated with normal follicular waves of 6 to 8 days.

Ovarian follicular cysts tend to develop in the first 20 to 30 days postpartum in 20 to 30% of cows (Butler, 2004; Vanholder et al., 2006). However, 50% (Roth et al., 2012) to 65% (Garverick, 1997) of these early cysts spontaneously cure before 40 days postpartum and ovarian cyclicity resumes. On average, OFC persist for 13 days, but they may regress and new cysts form (Vanholder, et al., 2006). Hooijer et al. (2001) reported in a large data set from 40 herds, an incidence of 6.3% based on postpartum examinations. Bartolome et al. (2005) reported an incidence of 9 to 25% for OFC. However, studies from Argentina and Norway report incidence rates under 2%. My personal experience has been OFC in cows after 30 days postcalving is less than 1.8%.

■ Diagnosis and Treatment

Ovarian follicular cysts were classically defined as a structure ≥25 mm in diameter that persisted on the ovary for at least 10 days in the absence of a CL. Historically, rectal palpation was the method of choice for detection of OFC. However, rectal palpation has a low sensitivity and specificity for diagnosis (Douthwaite and Dobson, 2000). In addition, luteinization of the cyst wall (luteal cyst) cannot be readily detected by rectal palpation. Behavioural changes were used to suggest OFC if cows exhibited nymphomania behavior, but a majority of cystic cows are anestrus. Rectal examination using ultrasound imaging with a 7.5 MHz linear array probe has become the method of choice. However ancillary tests for serum progesterone are also useful.

Currently, the classic definition for a cyst has come under criticism. Halter et al. (2003) have recommended an OFC be defined as a fluid filled structure ≥17 mm in diameter that persists on the ovary for 6 days. Bartolome et al. (2005) have adopted a similar definition, but include multiple fluid filled structures ≥ 17 mm in diameter that persist for 6 days. A problem with these definitions is that ovulatory follicles may be >20 mm in size (20% of follicles reported by Wiltbank et al., 2002), thereby classifying ovulatory follicles as cysts. Accurately characterizing pathology of OFC is made difficult due to the variation in definition across studies, and the further difficulty in following OFC development prospectively postcalving.

Treatments for OFC include GnRH or GnRH analogs, human chorionic gonadotropin (hCG) or other LH type preparations, progesterone, and PGF2α (Ambrose et al., 2004; Douthwaite and Dobson, 2000; Probo et al., Trebble et al., 2001; Vanholder et al. 2006). An injection of GnRH initiates a release of LH from the pituitary. In about 50% of cows, a dominant follicle ovulates after GnRH and a new follicular wave is initiated with subsequent ovulation in 6 to 8 days. The follicular cyst does not ovulate but luteinizes in the majority of

cases treated with GnRH. In 80 to 90% of cows given GnRH, progesterone rises, hypothalamic sensitivity to estradiol is restored, and ovulation and estrous cycles commence in 21 to 25 days. Prostaglandin F2α may be given 7 to 14 days post GnRH injection to hasten time to next estrus. Conception rate is usually somewhat lower at the subsequent estrus than in “normal” cows. Insertion of a CIDR or some other progesterone device for 7 to 9 days following the GnRH injection can enhance fertility at the subsequent estrus.

The most effective management strategy to control pregnancy in anovulatory cows is employing a PreSynch-OvSynch program to manage reproduction (Pursley et al. 1995). At least 20% of anovulatory cows will become pregnant at first timed insemination. Fertility will improve with subsequent cycles.

■ Conclusions

Ovulatory dysfunction may affect 10 to 50% of dairy cows within a herd. Cows that fail to ovulate by 40 to 60 days postpartum have reduced fertility. Nutritional and metabolic stress, infectious disease, inflammation, and stress in general are risk factors associated with the condition. Ovulatory dysfunction may present as sequential waves of dominant follicles that fail to ovulate or as ovarian cystic structures. Good transition cow management and nutrition can minimize the condition.

■ References

Ambrose, D. J., E. J-P. Schmidt, F. L. Lopes, R. C. Mattos, and W. W. Thatcher. 2004. Ovarian and endocrine responses associated with the treatment of cystic ovarian follicles in dairy cows with gonadotropin releasing hormone and prostaglandin F 2α, with or without exogenous progesterone. Can. Vet. J. 45:931-937.

Adams, G. P., R. Jaiswal, J. Singh, and P. Malhi. 2008. Progress in understanding ovarian follicular dynamics in cattle. Theriogenology 69:72-80.

Bartolome, J.A., W.W. Thatcher, P. Melendez, C. A. Risco, and L. F. Archibald. 2005. Strategies for the diagnosis and treatment of ovarian cysts in dairy cattle. J. Am. Vet. Med. Assoc. 227:1409-1414.

Beam, S. W and W. R. Butler. 1997. Energy balance and ovarian follicle development prior to the first ovulation postpartum in dairy cows receiving three levels of dietary fat. Biol. of Reprod. 56;133-142.

Beam, S. W. and W. R. Butler. 1999. Effects of energy balance on follicular development and first ovulation in postpartum dairy cows. J. of Reprod. Fert. Supplement 54:411-424.

Butler, W. R. 2003. Energy balance relationships with follicular development, ovulation and fertility in postpartum dairy cows. Livest. Prod. Sci. 83:211-218.

Butler, S. R., S. H. Pelton, and W. R. Butler. 2004. Insulin increases 17β-estradiol production by the dominant follicle of the first postpartum follicle wave in dairy cows. Reproduction 127:537-545.

Chong, S. H., O. G. Sá Filho, V. A. Absalón-Medina, S. H. Pelton, W. R. Butler, and R. O. Gilbert. 2015. Metabolic and endocrine differences between dairy cows that do or do not ovulate first postpartum dominant follicles. Biol. Reprod. DOI:10.1095/biolreprod.114.127076.

Douthwaite, R. and H. Dobson. 2000. Comparison of different methods of diagnosis of cystic ovarian disease in cattle and an assessment of its treatment with a progesterone-releasing intravaginal device. Vet. Rec. 147:355-359.

Garverick, H. A. 1997. Ovarian follicular cysts in dairy cows. J. Dairy Sci. 80:995-1004.

Halter, T. B., S. H. Hayes, L. F. Laranja da Fonseca, and W. J. Silvia. 2003. Relationship between endogenous progesterone and follicular dynamics in lactating dairy cows with ovarian follicular cysts. Biol. of Repro. 69:218-223.

Hein, G. J., C. G. Panzani, F. M. Rodriguez, N. R. Salvetti, P. U. Díaz, N. C. Gareis, G. A. Benítez, H. H. Ortega, and F. Rey. 2015. Impaired insulin signaling pathway in ovarian follicles of cows with cystic ovarian disease. Anim. Repro. Sci. 156:64-74.

Hooijer, G. A., M. A. A. J. van Oijen, K. Frankena, M. M. H. Valks. 2001. Fertility parameters of dairy cows with cystic ovarian disease after treatment with gonadotropin-releasing hormone. Vet. Rec. 149:383-386.

Peter, A. T. 2004. An update on cystic ovarian degeneration in cattle. Reprod. Dom. Anim. 39:1-7.

Peter, A. T., P. L. A. M. Vos, and D. J. Ambrose. 2009. Postpartum anestrus in dairy cattle. Theriogenology 71:1333-1342.

Probo, M., A. Comin, A. Mollo, F. Cairoli, G. Stradaioli, and M. C. Veronesi. Reproductive performance of dairy cows with luteal or follicular ovarian cysts after treatment with busrelin. Anim. Repro. Sci. 127:135-139.

Pursley, J. R., Mee, M. O., and Wiltbank, M. C. 1995. Synchronization of ovulation in dairy cows using PGF2α and GnRH. Theriogenology 44:915-923.

Rodriguez, F. M., N. R. Salvetti, C. G. Panzani, C. G. Barbeito, H. H. Ortega, and F. Rey. 2011. Influence of insulin-like growth factor-binding proteins-2 and -3 in the pathogenesis of cystic ovarian disease in cattle. Anim. Repro. Sci. 128:1-10.

Roth, Z., D. Biran, Y. Lavon, I. Dafni, S. Yakobi, and R. Braw-Tal. 2012. Endocrine milieu and development dynamics of ovarian cysts and persistent follicles in postpartum dairy cows. J. Dairy Sci. 95:1729-1737.

Silva, W. J., T. B. Halter, A. M. Nugent, L. F. Laranja da Fonseca. 2002. Ovarian follicular cysts in dairy cows: An abnormality in folliculogenesis. Dom. Anim. Endoc. 23:167-177.

Vanholder, T., J.L.M.R. Leroy, J. Dewulf, L. Duchateau, M. Coryn, A. de Kruif, and G. Opsomer. 2005. Hormonal and metabolic profiles of high-yielding

dairy cows prior to ovarian cyst formation or first ovulation post partum. Reprod. Dom. Anim. 40:460-467.

Vanholder, T., G. Opsomer, and A. De Kruif. 2006. Aetiology and pathogenesis of cystic ovarian follicles in dairy cattle. A review. Reprod. Nutr. Dev. 46:105-119.

Wiltbank MC, Gümen A, Sartori R. 2002. Physiological classification of anovulatory conditions in cattle. Theriogenology, 57:21-52.

Zwald, N. R., K. A. Weigel, Y. M. Chang, R. D. Welper, and J. S. Clay. 2004. Genetic selection for health traits using produer-recorded data. I. Incidence rates, heritability estimates, and sire breeding values. J. Dairy Sci. 87:4287-4294.