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Physiological characteristics and effects on fertility of the first follicular wave dominant follicle in cattle

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Abstract. The first follicular wave emerges soon after ovulation, and its dominant follicle (DF) develops during the first 8–10 days of the estrous cycle in cattle. And, the first-wave DF is a non-ovulatory follicle, because it develops during the first half of the estrous cycle simultaneously with the corpus luteum (CL), which produces and secretes progesterone. Regarding the characteristics of development and the mechanisms of deviation in the DF during the follicular wave, the first-wave DF has been well studied. However, the characteristics of the first-wave DF, such as growth, blood flow in the follicular wall, concentration of sex steroid hormones in the peripheral blood and follicular fluid, amounts of mRNA in granulosa cells, as well as the characteristics of the CL formed after the first-wave DF and the influence of the first-wave DF on fertility (conception rate), have not been well studied. Additionally, the first-wave DF synthesizes and secretes 17β-estradiol (E_2), and plasma E_2 concentration increases during the early stage of the estrous cycle. Consequently, there is a possibility that the first-wave DF might affect the fertility in cattle. In this review, to provide the new perspective on reproductive physiology in cattle, characteristics of the first-wave DF were examined in detail and its characteristics were compared with that of the second-wave DF. In addition, the locational effects of the first-wave DF and CL on conception rate are discussed.

Key words: Cattle, Conception rate, First follicular wave dominant follicle, Follicle dynamics, Granulosa cells

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Introduction

The reproductive performance of lactating dairy cows has been decreasing worldwide over the past few decades (conception rate: 55% *vs.* 45%, 1950s *vs.* 1998; calving interval: 13.5 months *vs.* 14.8 months, 1970 *vs.* 1999; services per conception rate: 1.62 *vs.* 2.91, 1972 *vs.* 1996) [1]. The decline in fertility has been attributed to various factors, such as lower estrous detection, housing systems, herd size, failure of nutritional management, and metabolic and diseased states [2, 3]. To improve the insemination rate, estrous synchronization programs have been used in reproductive management in the dairy and beef cattle industry [4–6]. However, to achieve a higher conception rate, we need a much deeper understanding of the characteristics of ovarian physiology and mechanisms of maternal recognition in high-producing dairy cows.

In cattle, the synchronous development of a group of 8–41 small follicles are observed in 2 to 3 times during an estrous cycle, and these groups developing follicles development are called as a follicular wave [7–10]. Further, the largest follicle that continues to grow during the follicular wave is defined as the dominant follicle (DF), whereas the other subordinate follicles go into atresia [11, 12]. The first follicular wave emerges soon after ovulation (day of ovulation = 0 day) and the first-wave DF grow 8–11 days of the estrous cycle; however, the first-wave DF becomes a non-ovulatory follicle because it develops during the first half of the estrous cycle simultaneously with the corpus luteum (CL) [9] (Fig. 1). In estrous cycles with a two-wave follicular wave pattern, the second wave emerges on 9–11 days of the estrous cycle, and the second-wave DF becomes an ovulatory follicle [13]. On the other hand, with a three-wave follicular wave pattern, the second-wave emerges on 8–9 days of the estrous cycle, and the third-wave emerges 15–16 days of the estrous cycle, and the third-wave DF becomes an ovulatory follicle [13]. Although the timing of luteolysis (two-wave *vs.* three-wave: 16 days *vs.* 19 days) and duration of the estrous cycle (two-wave *vs.* three-wave: 19–20

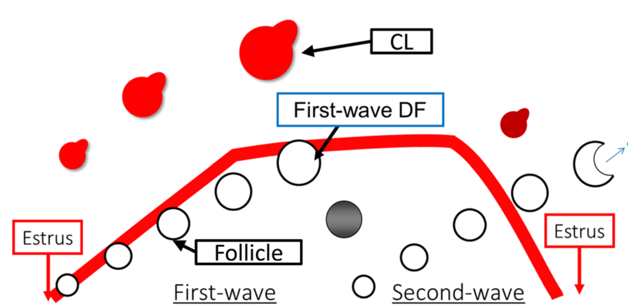

Fig. 1. Schematic figure of dynamics of dominant follicle (DF) and corpus luteum (CL) during estrous cycle (two-waves of follicular wave pattern).

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days *vs.* 22–23 days) differ between the two-wave and three-wave patterns [13], the first follicular wave emerges soon after estrus and it becomes a non-ovulatory follicle in both of the two-wave and three-wave patterns.

Regarding the characteristics of DF development and the mechanisms of selection of DF during the follicular wave, the first-wave DF has been well studied [14–17]. However, the characteristics of the first-wave DF and the influence of the first-wave DF on fertility (conception rate) have not been thoroughly investigated.

In previous studies, the concentration of 17β-estradiol (E_2) in follicular fluid and the production of androstenedione (A_4) and progesterone (P_4) by cultured theca cells were greater in the first-wave DF than in the second-wave DF [18]. In addition, blood flow (BF) in the follicular wall of the preovulatory follicle is greater during the first wave than during the second wave [19]. Therefore, it is hypothesized that the characteristics of the first-wave DF differ in comparison to those of the second-wave DF.

The effects of the first-wave DF on conception rate have not been well investigated. However, the first-wave DF synthesizes E_2 [14], and the plasma E_2 concentration increases during the early stage (4–5 days) of the estrous cycle [20]. Consequently, there is a possibility that the first-wave DF might affect fertility in cattle.

In this review, we will discuss 1) the characteristics of the first-wave DF, such as growth, blood flow in the follicular wall, amounts of sex steroid hormones and mRNA in the peripheral blood and follicular fluids, and formation of the CL, and 2) the influence of the first-wave DF on fertility, in particular, the relationship between the location of the first-wave DF and CL in the ovary and the effects on conception rate.

Follicle Development, Blood Flow in the Follicular Wall and Plasma E_2 Concentration in the First-wave DF

To determine the characteristics of first-wave DF development, the diameter, blood flow in the follicular wall and plasma E_2 concentration ware compared with those of the second-wave DF using hormonal treatment (prostaglandin $F_{2\alpha}$ [$PGF_{2\alpha}$] and gonadotropin-releasing hormone [GnRH]) to induce estrus and ovulation in non-lactating Holstein cows [21].

In this experiment, spontaneous ovulation day (emergence of the first-wave) was defined as Day 0 in the first-wave group. On the other hand, to mimic second-wave emergence, spontaneous ovulation was defined as Day −7, and GnRH was administrated on Day −2 to induce ovulation of the first-wave DF, and we confirmed ovulation on Day 0 (emergence of the second-wave). Then, we administrated $PGF_{2\alpha}$ on Day 6 and GnRH on Day 8 to induce estrus and ovulation in the first- and second-wave DF. Therefore, a similar time axis of the duration of follicular growth and timing of maturation existed between the first- and second-wave of follicular development and the maturation and changes occurring before ovulation were compared between the first- and second-wave DF.

The diameter of the first-wave DF was larger on Day 6 than on Day 3; however, the diameter of the second-wave DF was not significantly different between Days 3 to 6. After $PGF_{2\alpha}$ treatment, the diameter of the first-wave DF increased between Days 6 and 8, but no increase was observed in the second-wave DF. The diameter of the first-wave DF on Days 8 and 9 was larger than in that of the second-wave DF (Fig. 2). Blood flow in the follicular wall (BFA, blood flow area; BF%, the percentage of the follicular circumference with blood flow signals) was greater in the first-wave DF than in the second-wave DF on Day 9 (Fig. 3). Plasma E_2 concentration was higher on Day 8 ($P < 0.01$) in the first-wave (7.5 ± 0.9 pg/ml) than in the second-wave DF (4.4 ± 0.5 pg/ml).

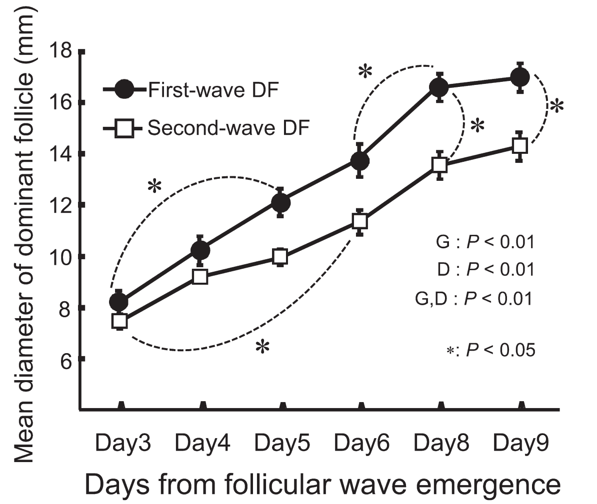

Fig. 2. Comparative changes of mean diameter of the first-wave DF and the second-wave DF between Day 3 to Day 9. Day 0 = day of follicular wave emergence. The asterisk denotes difference between each point, * $P < 0.05$. Values are mean ± SEM of each point. Modified from [21].

Luteinizing hormone (LH) is necessary for the development of the DF [16]. A higher LH pulse frequency has been observed in cattle with a basal concentration of P_4 [22]. Because plasma P_4 concentration is lower during the Days 0 to 6 in the first-wave than in the second-wave [21], the frequency of the LH pulse may have been higher in the first-wave than in the second-wave during the development of the DF, and this endocrine condition may lead to the larger size of the DF in the first-wave relative to that of the second wave.

The greater BF%, which represents the degree of distribution of blood flow signals in the follicular wall, in the first-wave DF on Day 9 could indicate that the blood vessels in the follicular wall were more widely distributed than that in the second-wave DF. Therefore, it is likely that the greater blood flow area in the first-wave DF might be caused by greater vascularity in the follicular wall. However, we could not clarify the reason for higher plasma E_2 concentration in the first-wave DF than in the second-wave DF from these results.

Follicular Fluid E_2 and A_4 Concentrations and Amount of mRNA Expression in the Granulosa Cells

To elucidate the reason for higher plasma E_2 concentration in the first-wave DF compared with that of the second-wave DF and evaluate the features of the first-wave DF in more detail, aspiration of follicular fluid and collection of granulosa cells were performed

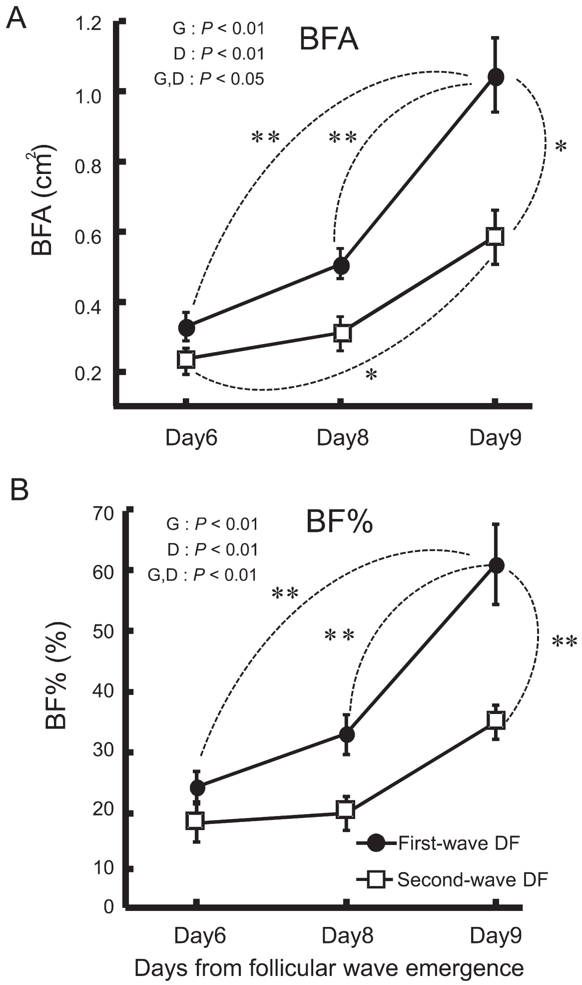

Fig. 3. Comparative changes of (A) blood flow area (BFA), (B) The percentage of follicle circumference with blood flow signals (BF%) at Day 6, 8 and 9 in the first-wave DF and the second-wave DF. Cows were treated with $PGF_{2\alpha}$ and GnRH at Day 6 and Day 8, respectively. Day 0 = day of follicular wave emergence. The asterisk denotes difference between each point, * $P < 0.05$, ** $P < 0.01$. Values are mean ± SEM of each point. Modified from [21].

Table 1. The 17β-estradiol (E_2) and androstenedione (A_4) concentrations in follicular fluid on Day 8 [a]

	First-wave DF [b]	Second-wave DF	P-value
E_2 (ng/ml)	1942.4 ± 247.9	1169.3 ± 90.9	P < 0.05
A_4 (ng/ml)	161.8 ± 26.2	104.6 ± 12.7	P < 0.05

Modified from [21]. Values are means ± SEM. [a] Day 8 = the day of gonadotropin-releasing hormone (GnRH) treatment. [b] DF = dominant follicle.

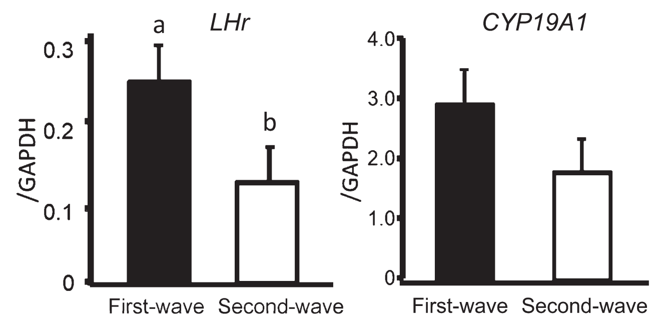

Fig. 4. *LHr* and *CYP19A1* mRNA amounts of granulosa cells of DF on Day 8. In each figure, the black bar indicates the first-wave DF and the white bar indicates the second-wave DF. Day 0 = day of follicular wave emergence. Different letters indicated $P < 0.05$. Values are shown as mean ± SEM. Modified from [21].

from DF during estrus (Day 8) and the preovulatory period (Day 9) in non-lactating Holstein cows [21, 23]. The experimental protocol was same as that in the experiment described above; therefore, the DF at Day 8 was two days after the $PGF_{2\alpha}$ treatment, before the LH surge, and the DF at Day 9 was one day after the GnRH treatment, after the LH surge.

Follicular fluid E_2 and A_4 concentrations were higher in the first-wave than in the second-wave DF (Table 1). Amount of *LHr* mRNA expression on Day 8 was higher in the first-wave DF than in the second-wave DF; however, *CYP19A1* mRNA expression did not differ between the first and second wave (Fig. 4). On Day 9, amounts of *VEGF120*, *FGF-2* and *StAR* tended to be higher in the first-wave DF than in the second-wave DF. *VEGF164*, *P450-scc*, and *3β-HSD* were higher in the first-wave DF than in the second-wave DF (Fig. 5).

The limiting factor for E_2 synthesis in the follicle is the production of A_4 in the theca cells rather than the P450 aromatase activity [14]. A_4 is produced in theca cells and transported to granulosa cells as an E_2 precursor [24]. Wolfenson *et al.* [18] reported that the productions of A_4 and P_4 by cultured theca cells were greater in the first-wave DF compared with those of the second-wave DF. A greater concentration of A_4 in follicular fluid was observed in the first-wave DF. Consequently, the main reason for the higher E_2 concentration in follicular fluid of the first-wave DF may be the higher production of A_4 in theca cells; therefore, plasma E_2 level is higher on Day 8 in the first-wave.

Luteinizing hormone induces gene expression of *LHr* in the granulosa cells of cattle [25]. The frequency of the LH pulse may be greater in the first-wave than in the second-wave during the development of the DF because of a lower concentration of P_4 [21]. A higher LH pulse frequency might lead to higher *LHr* mRNA expression. It was presumed that the first-wave DF was more responsive to the LH surge, which may lead to higher mRNA expressions of *VEGF120*, *FGF-2*, *VEGF164*, *StAR, P450-scc*, and *3β-HSD* in the granulosa cells.

These results indicated that the growth, blood flow supply, and steroidogenesis were more active in the first-wave DF than in the second-wave DF.

Growth, Blood Flow, and Plasma P_4 Concentration in the CL Formed after Ovulation of the First-wave DF

Amounts of angiogenic and steroidogenic factors were greater

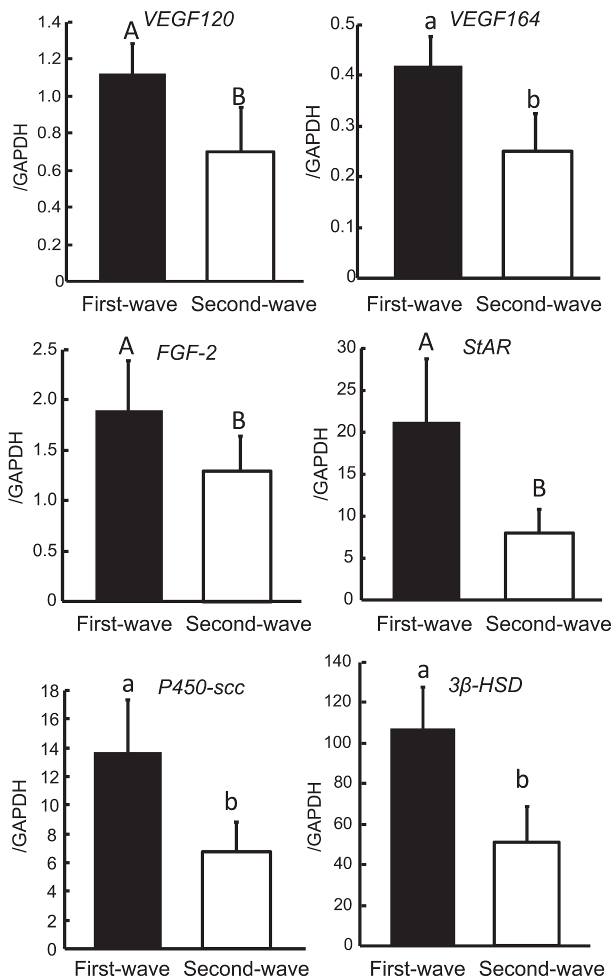

Fig. 5. *VEGF120*, *VEGF164, FGF-2*, *StAR*, *P450-scc* and *3β-HSD* mRNA amounts of granulosa cells of DF on Day 9. In each figure, the black bar indicates the first-wave DF and the white bar indicates the second-wave DF. Day 0 = day of follicular wave emergence. Significant differences are indicated by letters; $^{A, B}$ $P < 0.1$, $^{a, b}$ $P < 0.05$. Values are shown as mean ± SEM. Modified from [23].

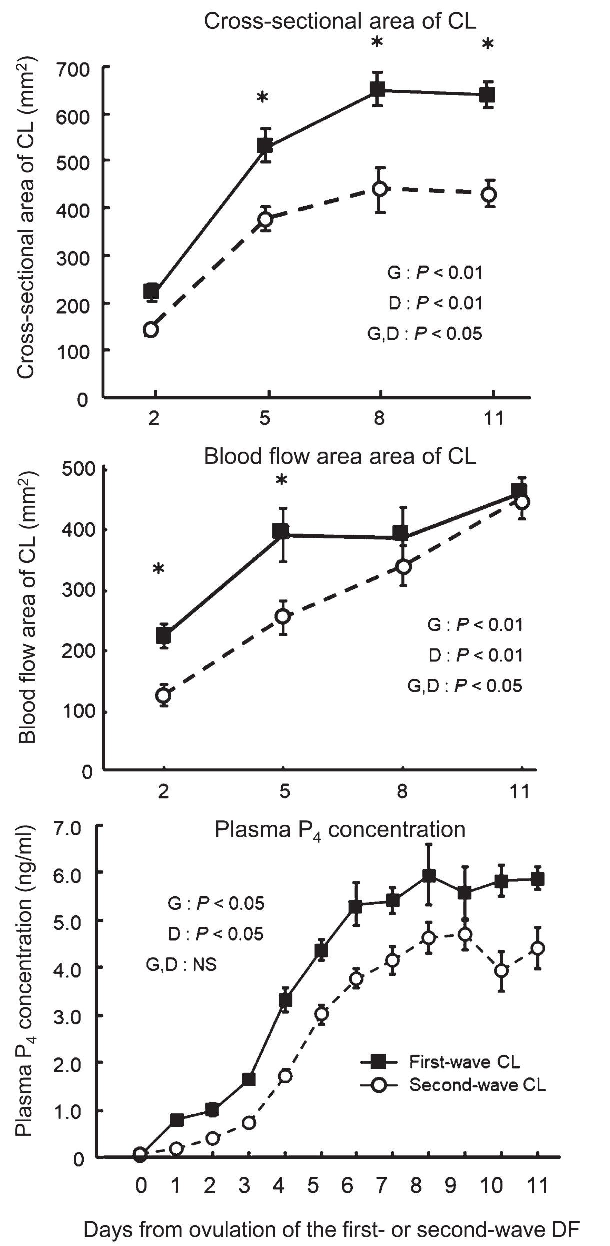

Fig. 6. Comparative changes of cross-sectional and blood flow areas of corpus luteum (CL), and blood progesterone (P_4) levels in first or second-wave CL. X axis showed days from ovulation of the first- or second-wave DF. The asterisk denotes difference between each point of same day, * $P < 0.05$. Values are mean ± SEM of each point. Modified from [23].

in the first-wave DF than in the second-wave DF. Therefore, the luteinization process may be more active during the first-wave DF after the LH surge. It was hypothesized that the CL that formed after ovulation of the first-wave DF has a greater size and greater steroidogenic capacity; therefore, we investigated the growth, blood flow, and plasma P_4 concentration in the CL formed after ovulation of the first-wave DF in comparison with that of the second-wave.

The cross-sectional area of the CL, blood flow area in the CL, and plasma P_4 concentration were higher in the CL formed after ovulation of the first-wave DF than after the second-wave DF (Fig. 6).

In a previous study, the local administration of a VEGF antagonist (soluble VEGF receptor) into the preovulatory follicle impaired the subsequent structure and function of the CL [26]. Furthermore, treatment with an FGFR1 inhibitor using bovine luteal cells caused a maximal reduction in the total area of the endothelial cell networks and reduced the total number of branch points and degree of branching per endothelial cell island [27]. Expression levels of *VEGF120*, *VEGF164*, and *FGF-2* were higher in granulosa cells of the first-wave DF than the second-wave DF. This may lead to higher blood flow area and size of the CL formed after ovulation of the first-wave DF.

Progesterone is synthesized in luteal cells by several steroidogenic enzymes such as StAR, P450-scc and 3β-HSD [28]. *StAR*, *P450-scc*,

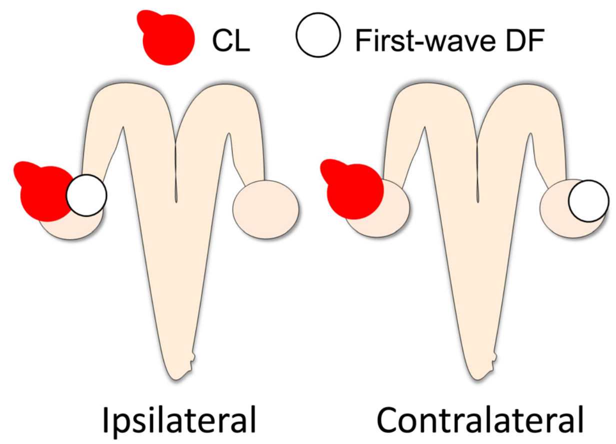

Fig. 7. Schematic figure of the locational relationship between the first-wave dominant follicle (DF) and corpus luteum (CL).

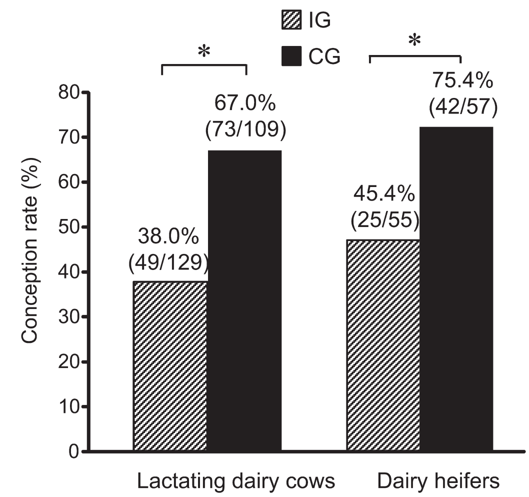

Fig. 8. Conception rates in ipsilateral group (IG) and contralateral group (CG). The asterisk denotes difference between each point of same day, * $P < 0.01$. Modified from [30].

and *3β-HSD* mRNA in granulosa cells were higher in the first-wave DF than the second-wave DF; therefore, it was expected that the steroidogenic capacity of the luteal cells would be greater in the first-wave CL than that in the second-wave CL. In addition, size of the first-wave CL was larger than that of the second-wave CL. Taking these findings together, greater steroidogenesis and size in CL formed after ovulation of the first-wave DF may lead to a greater plasma concentration of P_4.

Thus, ovulation of the preovulatory follicle of the first-wave DF leads to the formation of a more active CL than that of the second-wave DF.

Conception Rates between the First-wave DFs that are Ipsilateral and Contralateral to the CL in the Ovaries

The dynamics of DF growth and the hormonal milieu during first-wave development have been well studied [13]. However, the influence of the first-wave DF on fertility (conception rate) in cattle remains unclear. Furthermore, the first-wave DF develops contralateral or ipsilateral to the CL (Fig. 7). In a previous study, the relative locations of the first-wave DF and CL were determined, and the number of follicular waves with the DF and CL ipsilateral or contralateral to the ovaries did not vary during the first-wave [29]. However, the locational effects of the first-wave DF that is contralateral or ipsilateral to the CL on fertility remains unevaluated. Therefore, we compared conception rates between the first-wave DF that were ipsilateral and contralateral to the CL in the ovaries of lactating dairy cows and dairy heifers [30].

A total of 238 artificial inseminations (AIs) in lactating dairy cows [average postpartum day of AI, 119.8 ± 5.2; average parity, 2.2 ± 0.1; average milk production, 33.9 ± 0.5 kg/day; average body condition score (BCS), 2.91 ± 0.02; average live weight, 637.4 ± 4.6 kg; mean ± SEM] and 112 AIs in dairy heifers (average age, 14.2 ± 0.3 months; average live weight, 440.6 ± 5.0 kg) were analyzed. These replicates underwent regular estrous cycles and were clinically healthy during the breeding period. If the lactating dairy cow experienced reproductive or metabolic diseases, we excluded it from the study.

The location of the first-wave DF in the ovary was confirmed at that time to be ipsilateral (ipsilateral group, IG) or contralateral (contralateral group, CG) to the CL during Day 5 to 9 after AI. Conception rates were 54.0% in all cattle, 48.9% in lactating dairy cows and 58.9% in dairy heifers.

Conception rates were lower in IG than in CG of both of lactating dairy cows and dairy heifers (lactating dairy cows, 38.0% *vs.* 67.0%; dairy heifers, 45.5% *vs.* 75.4%; IG *vs.* CG: Fig. 8.). Additionally, we analyzed the effect of season, days in milk at AI, milk production, body condition score, parity, or live weight on conception rate, but these factors did not affect conception rates in either group in this study.

The endometrium of the uterine horn in cattle, which is located on the same side of the ovary as the CL, has a higher P_4 concentration compared with that of the endometrium in the opposite uterine horn [31, 32]. In addition, the concentration of E_2 in the oviduct ipsilateral to the preovulatory follicle is higher than that of the one contralateral to the preovulatory follicle in bovine [33]. These results indicate that there is a strong local interaction between the uterine horn and the same side ovary. The first-wave DF produces and secretes E_2 during follicular development in cows [20]. Therefore, it is hypothesized that E_2 secreted from the first-wave DF may locally affect the same side of the uterine horn and/or oviduct and affect the function of the reproductive tract, which was associated with decreased fertility in IG. However, the mechanism of lower fertility when the first-wave DF is ipsilateral to the CL remains unclear. We require further research to evaluate the steroid hormones, such as P_4 and E_2, concentrations and mRNA expression of steroid hormone receptors in oviduct and the endometrium of IG and CG.

Consequently, the locational relationship of the first-wave DF and CL affects the conception rate after AI, in particular, ipsilateral location relative to the CL in the ovary was associated with reduced conception rates in both lactating dairy cows and dairy heifers.

Effect of hCG Treatment 5 Days after AI on the Conception Rate in Ipsilateral and Contralateral Situations

Human chorionic gonadotropin (hCG) has a luteinizing hormone-like effect in cattle [34]. During the early luteal phase, hCG induces ovulation of the first wave DF and the formation of an accessory CL, with a subsequent increase in plasma P_4 concentrations in cattle [35]. On the basis of the increased plasma P_4 concentrations, several trials of hCG treatment after AI in the early luteal phase of lactating dairy cows have been performed to increase conception rates [36]. However, the effects of hCG administration on fertility are not consistent between studies [37, 38]. From the results of previous chapter, the development of the first-wave DF in the ovary ipsilateral to the CL was associated with reduced conception rates in lactating dairy cows. On this basis, removing the first-wave DF that develops ipsilateral to the CL using hCG treatment could eliminate the detrimental effects on fertility, and thereby, possibly increase conception rates [39].

We performed 599 AIs in lactating dairy cows in four dairy farms (postpartum day of AI, 125.4 ± 62.6; parity, 2.4 ± 1.5; means ± SD). Cows underwent regular estrous cycles and were clinically healthy during the breeding period. Cows that experienced reproductive or metabolic diseases were excluded. They were randomly assigned to either the non-treatment group or hCG treatment group 5 days after AI. The cows in the non-treatment group (n = 363) were not administrated hCG after AI, whereas those in the hCG treatment group (n = 214) were intramuscularly administrated 1500 IU hCG 5 days after AI. In addition, the location of the first-wave DF in the ovary was confirmed to be either ipsilateral (IG: non-treatment, n = 220; hCG treatment, n = 128) or contralateral (CG: non-treatment, n = 143; hCG treatment, n = 86) to the CL.

Conception rate increased in the hCG treatment group with the IG (40.6%) more than in the non-treatment group with the IG (21.4%); however, there was no difference in the non-treatment (51.7%) and hCG treatment (43.0%) groups with the CG (Fig. 9). Parity, farm, days in milk at AI, interaction between the farm and hCG treatment, and interaction between the farm and location of the first-wave DF and CL did not affect conception rate.

The physiological mechanisms of increasing conception rate by hCG treatment in IG were not completely clarified in this study. In a previous study, lactating dairy cows that were diagnosed as pregnant have a higher P_4 concentration from 6 to 8 days after AI compared to that of non-pregnant cows [40]. However, plasma P_4 concentration was not different between IG and CG in lactating dairy cows (unpublished data). Thus, the higher conception rate in CG compared to IG might be not caused by a greater plasma P_4 concentration in CG than IG. It is possible that E_2 secreted from the first-wave DF might have locally affected the same side of the uterine horn or oviduct and affected the function of the reproductive tract. Because ovulation of the first-wave DF in the IG condition with hCG treatment could eliminate the detrimental effects on fertility, the conception rate increased in IG. On the contrary, it has been reported that the P_4 concentration in the endometrial tissue is higher in the ipsilateral location of the CL in the ovary [31, 32]. Therefore, because hCG treatment with the IG condition had an accessory CL

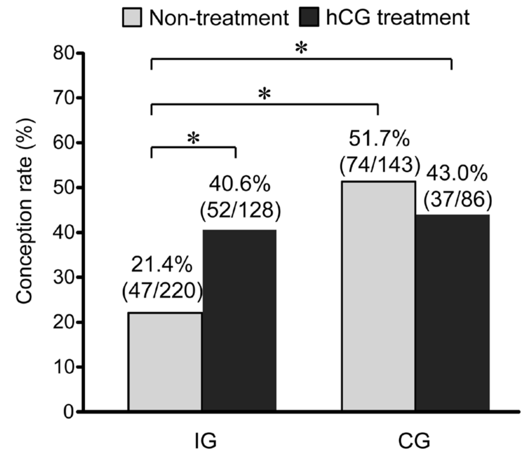

Fig. 9. Effect of hCG treatment 5 days after AI on the conception rate in ipsilateral group (IG) and contralateral group (CG). The asterisk denotes difference between each point of same day, * $P < 0.01$.

and original CL in the same side of the ovary, the P_4 concentration in the oviduct and uterine horn under the ipsilateral condition of the CL might be higher and have a positive effect on fertility compared with the IG condition with no hCG treatment.

However, we could not evaluate the purely local negative effect of the first-wave DF on fertility. Further research is warranted to verify the locational effect of the first-wave DF on fertility following follicle aspiration after AI.

From the present study of lactating dairy cows, it was shown that hCG treatment 5 days after AI had a beneficial effect on fertility only when the first-wave DF developed ipsilateral to the CL in the ovary, and not when the first-wave DF developed contralaterally.

Conclusion

We showed that 1) compared to the second-wave DF, the first-wave DF had greater size, blood flow in the follicular wall, plasma E_2 concentration, follicular fluid E_2 and A_4 and mRNA expression *(LHr, VEGF, FGF-2, StAR, P450-scc, 3β-HSD*) when estrus was induced by hormonal treatment, 2) the CL formed after ovulation was greater in terms of size, blood flow, and plasma P_4 concentration in the first-wave DF than in the second-wave DF, 3) the first-wave DF located ipsilateral to the CL in the ovary was associated with reduced conception rates, and 4) hCG treatment 5 days after AI had a beneficial effect on fertility only when the first-wave DF developed ipsilateral to the CL in the ovary, and not when the first-wave DF developed contralaterally. Further studies are needed to clarify the physiological mechanism of these phenomena. We suggest that progress in such research would provide new perspectives on the reproductive physiology of cattle and the development of clinical applications for improvement of reproductive performance in the cattle industry.

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References

1. **Lucy MC.** Reproductive loss in high-producing dairy cattle: where will it end? *J Dairy Sci* 2001; **84**: 1277–1293. [Medline] [CrossRef]
2. **López-Gatius F.** Factors of a noninfectious nature affecting fertility after artificial insemination in lactating dairy cows. A review. *Theriogenology* 2012; **77**: 1029–1041. [Medline] [CrossRef]
3. **Shahinfar S, Page D, Guenther J, Cabrera V, Fricke P, Weigel K.** Prediction of insemination outcomes in Holstein dairy cattle using alternative machine learning algorithms. *J Dairy Sci* 2014; **97**: 731–742. [Medline] [CrossRef]
4. **Bisinotto RS, Ribeiro ES, Santos JE.** Synchronisation of ovulation for management of reproduction in dairy cows. *Animal* 2014; **8**(Suppl 1): 151–159. [Medline] [CrossRef]
5. **Carvalho PD, Santos VG, Giordano JO, Wiltbank MC, Fricke PM.** Development of fertility programs to achieve high 21-day pregnancy rates in high-producing dairy cows. *Theriogenology* 2018; **114**: 165–172. [Medline] [CrossRef]
6. **Bó GA, de la Mata JJ, Baruselli PS, Menchaca A.** Alternative programs for synchronizing and resynchronizing ovulation in beef cattle. *Theriogenology* 2016; **86**: 388–396. [Medline] [CrossRef]
7. **Pierson RA, Ginther OJ.** Ultrasonic imaging of the ovaries and uterus in cattle. *Theriogenology* 1988; **29**: 21–37. [CrossRef]
8. **Sirois J, Fortune JE.** Ovarian follicular dynamics during the estrous cycle in heifers monitored by real-time ultrasonography. *Biol Reprod* 1988; **39**: 308–317. [Medline] [CrossRef]
9. **Ginther OJ, Knopf L, Kastelic JP.** Temporal associations among ovarian events in cattle during oestrous cycles with two and three follicular waves. *J Reprod Fertil* 1989; **87**: 223–230. [Medline] [CrossRef]
10. **Burns DS, Jimenez-Krassel F, Ireland JL, Knight PG, Ireland JJ.** Numbers of antral follicles during follicular waves in cattle: evidence for high variation among animals, very high repeatability in individuals, and an inverse association with serum follicle-stimulating hormone concentrations. *Biol Reprod* 2005; **73**: 54–62. [Medline] [CrossRef]
11. **Ginther OJ, Wiltbank MC, Fricke PM, Gibbons JR, Kot K.** Selection of the dominant follicle in cattle. *Biol Reprod* 1996; **55**: 1187–1194. [Medline] [CrossRef]
12. **Ginther OJ, Beg MA, Bergfelt DR, Donadeu FX, Kot K.** Follicle selection in monovular species. *Biol Reprod* 2001; **65**: 638–647. [Medline] [CrossRef]
13. **Adams GP, Jaiswal R, Singh J, Malhi P.** Progress in understanding ovarian follicular dynamics in cattle. *Theriogenology* 2008; **69**: 72–80. [Medline] [CrossRef]
14. **Badinga L, Driancourt MA, Savio JD, Wolfenson D, Drost M, De La Sota RL, Thatcher WW.** Endocrine and ovarian responses associated with the first-wave dominant follicle in cattle. *Biol Reprod* 1992; **47**: 871–883. [Medline] [CrossRef]
15. **Xu Z, Garverick HA, Smith GW, Smith MF, Hamilton SA, Youngquist RS.** Expression of messenger ribonucleic acid encoding cytochrome P450 side-chain cleavage, cytochrome p450 17 alpha-hydroxylase, and cytochrome P450 aromatase in bovine follicles during the first follicular wave. *Endocrinology* 1995; **136**: 981–989. [Medline] [CrossRef]
16. **Ginther OJ, Bergfelt DR, Beg MA, Kot K.** Follicle selection in cattle: role of luteinizing hormone. *Biol Reprod* 2001; **64**: 197–205. [Medline] [CrossRef]
17. **Sartori R, Fricke PM, Ferreira JC, Ginther OJ, Wiltbank MC.** Follicular deviation and acquisition of ovulatory capacity in bovine follicles. *Biol Reprod* 2001; **65**: 1403–1409. [Medline] [CrossRef]
18. **Wolfenson D, Sonego H, Shaham-Albalancy A, Shpirer Y, Meidan R.** Comparison of the steroidogenic capacity of bovine follicular and luteal cells, and corpora lutea originating from dominant follicles of the first or second follicular wave. *J Reprod Fertil* 1999; **117**: 241–247. [Medline] [CrossRef]
19. **Jordan A, Herzog K, Ulbrich SE, Beindorff N, Honnens A, Krüger L, Miyamoto A, Bollwein H.** Genital blood flow and endometrial gene expression during the preovulatory period after Prostaglandin F(2alpha)-induced luteolysis in different luteal phases in cows. *J Reprod Dev* 2009; **55**: 309–315. [Medline] [CrossRef]
20. **Savio JD, Thatcher WW, Badinga L, de la Sota RL, Wolfenson D.** Regulation of dominant follicle turnover during the oestrous cycle in cows. *J Reprod Fertil* 1993; **97**: 197–203. [Medline] [CrossRef]
21. **Miura R, Haneda S, Lee HH, Miyamoto A, Shimizu T, Miyahara K, Miyake Y, Matsui M.** Evidence that the dominant follicle of the first wave is more active than that of the second wave in terms of its growth rate, blood flow supply and steroidogenic capacity in cows. *Anim Reprod Sci* 2014; **145**: 114–122. [Medline] [CrossRef]
22. **Bergfeld EG, Kojima FN, Cupp AS, Wehrman ME, Peters KE, Mariscal V, Sanchez T, Kinder JE.** Changing dose of progesterone results in sudden changes in frequency of luteinizing hormone pulses and secretion of 17 β-estradiol in bovine females. *Biol Reprod* 1996; **54**: 546–553. [Medline] [CrossRef]
23. **Miura R, Haneda S, Matsui M.** Ovulation of the preovulatory follicle originating from the first-wave dominant follicle leads to formation of an active corpus luteum. *J Reprod Dev* 2015; **61**: 317–323. [Medline] [CrossRef]
24. **Fortune JE.** Bovine theca and granulosa cells interact to promote androgen production. *Biol Reprod* 1986; **35**: 292–299. [Medline] [CrossRef]
25. **Luo W, Gumen A, Haughian JM, Wiltbank MC.** The role of luteinizing hormone in regulating gene expression during selection of a dominant follicle in cattle. *Biol Reprod* 2011; **84**: 369–378. [Medline] [CrossRef]
26. **Hazzard TM, Xu F, Stouffer RL.** Injection of soluble vascular endothelial growth factor receptor 1 into the preovulatory follicle disrupts ovulation and subsequent luteal function in rhesus monkeys. *Biol Reprod* 2002; **67**: 1305–1312. [Medline] [CrossRef]
27. **Woad KJ, Hunter MG, Mann GE, Laird M, Hammond AJ, Robinson RS.** Fibroblast growth factor 2 is a key determinant of vascular sprouting during bovine luteal angiogenesis. *Reproduction* 2012; **143**: 35–43. [Medline] [CrossRef]
28. **Diaz FJ, Anderson LE, Wu YL, Rabot A, Tsai SJ, Wiltbank MC.** Regulation of progesterone and prostaglandin F2alpha production in the CL. *Mol Cell Endocrinol* 2002; **191**: 65–80. [Medline] [CrossRef]
29. **Ginther OJ, Kastelic JP, Knopf L.** Intraovarian relationships among dominant and subordinate follicles and the corpus luteum in heifers. *Theriogenology* 1989; **32**: 787–795. [Medline] [CrossRef]
30. **Miura R, Haneda S, Kayano M, Matsui M.** Short communication: Development of the first follicular wave dominant follicle on the ovary ipsilateral to the corpus luteum is associated with decreased conception rate in dairy cattle. *J Dairy Sci* 2015; **98**: 318–321. [Medline] [CrossRef]
31. **Cerbito WA, Miyamoto A, Balagapo CR Jr, Natural NG, Miyazawa K, Sato K.** Prostaglandin E2 levels in uterine tissues and its relationship with uterine and luteal progesterone during the estrous cycle in dairy cows. *Theriogenology* 1994; **42**: 941–950. [Medline] [CrossRef]
32. **Takahashi H, Haneda S, Kayano M, Matsui M.** Differences in progesterone concentrations and mRNA expressions of progesterone receptors in bovine endometrial tissue between the uterine horns ipsilateral and contralateral to the corpus luteum. *J Vet Med Sci* 2016; **78**: 613–618. [Medline] [CrossRef]
33. **Wijayagunawardane MP, Miyamoto A, Cerbito WA, Acosta TJ, Takagi M, Sato K.** Local distributions of oviductal estradiol, progesterone, prostaglandins, oxytocin and endothelin-1 in the cyclic cow. *Theriogenology* 1998; **49**: 607–618. [Medline] [CrossRef]
34. **Price CA, Webb R.** Ovarian response to hCG treatment during the oestrous cycle in heifers. *J Reprod Fertil* 1989; **86**: 303–308. [Medline] [CrossRef]
35. **Schmitt EJ, Diaz T, Barros CM, de la Sota RL, Drost M, Fredriksson EW, Staples CR, Thorner R, Thatcher WW.** Differential response of the luteal phase and fertility in cattle following ovulation of the first-wave follicle with human chorionic gonadotropin or an agonist of gonadotropin-releasing hormone. *J Anim Sci* 1996; **74**: 1074–1083. [Medline] [CrossRef]
36. **Nascimento AB, Bender RW, Souza AH, Ayres H, Araujo RR, Guenther JN, Sartori R, Wiltbank MC.** Effect of treatment with human chorionic gonadotropin on day 5 after timed artificial insemination on fertility of lactating dairy cows. *J Dairy Sci* 2013; **96**: 2873–2882. [Medline] [CrossRef]
37. **Santos JE, Thatcher WW, Pool L, Overton MW.** Effect of human chorionic gonadotropin on luteal function and reproductive performance of high-producing lactating Holstein dairy cows. *J Anim Sci* 2001; **79**: 2881–2894. [Medline] [CrossRef]
38. **Hanlon DW, Jarratt GM, Davidson PJ, Millar AJ, Douglas VL.** The effect of hCG administration five days after insemination on the first service conception rate of anestrous dairy cows. *Theriogenology* 2005; **63**: 1938–1945. [Medline] [CrossRef]
39. **Miura R, Matsumoto N, Izumi T, Kayano M, Haneda S, Matsui M.** Effects of human chorionic gonadotropin treatment after artificial inseminations on conception rate with the first follicular wave dominant follicle in the ovary ipsilateral to the corpus luteum in lactating dairy cows. *J Reprod Dev* 2018; **64**: 485–488. [Medline] [CrossRef]
40. **Lopes AS, Butler ST, Gilbert RO, Butler WR.** Relationship of pre-ovulatory follicle size, estradiol concentrations and season to pregnancy outcome in dairy cows. *Anim Reprod Sci* 2007; **99**: 34–43. [Medline] [CrossRef]