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EARLY EMBRYONIC LOSS IN DAIRY CATTLE AND THE SEARCH FOR HORMONAL THERAPY OR OTHER MANAGEMENT MEASURES TO IMPROVE IT

The most recent issue of the Journal of Dairy Science has several papers regarding decreased fertility in dairy cattle, and the efforts to develop hormonal treatment regimens to improve fertility. Much of the recent work focuses on trying to reduce loss of fetuses during early pregnancy. This prompted me to search the literature about this extensive and important subject area. I suspect that Utah is at least as much affected as are other parts of the country by the phenomenon that particularly during the hot summer, dairy producers find getting and keeping cows pregnant a constant challenge, if not outright frustrating.

There are numerous papers with data showing that during approximately the last 30 years, since the mid-1970's, all measures of dairy cattle fertility including time to first service, services/conception, maintenance of early pregnancy, percentage pregnant by a certain time such as 150 DIM, and days open (this number includes only pregnant cows and should never be the sole way to monitor reproductive performance in a herd) are worsening in Holsteins and Jerseys.

As dairy cows have been selected and fed for higher dry matter intake and milk production, there has been an associated decrease in circulating progesterone concentration in the cows. A paper by JS Stevenson et al., Journal of Dairy Science, July 2008 explains that serum progesterone concentration before AI is positively correlated with conception rate; progesterone concentrations greater than 5 ng/ml have been associated with conception rates improving from approximately 45% in cows below that level to approximately 65%. The article also mentions that previous studies, including some by R. Sartori et al., have found that as dairy cattle age, their ovulatory follicles and ovarian structures become larger than in heifers, but serum progesterone levels are lower than would be expected based upon CL size.

CIDR Inserts

The above findings have led to interest in controlled internal drug-release (CIDR) inserts, intravaginal progesterone releasing devices, for approximately 20 years. A study by A Iwakuma at al., reported in Journal of Veterinary Medical Science, March 2008, found that Holstein heifers treated with either Ovsynch or Heatsynch programs had a 63.9% pregnancy rate with CIDR treatment vs. 21.1% in heifers not treated with CIDR. However, results were confusing because CIDR was not associated with higher serum progesterone concentration, including whether it was above or below 5 ng/ml, but CIDR treated animals had more functional CL 7 days after the introduction of the intravaginal device, 3 d before insemination (10 d after CIDR application), 64.5% vs. 21.4%. (Note how close the functional CL numbers are to the pregnancy rate, but there was not a perfect relationship between functional CL and pregnancy). Another of the most recent papers, by DS Son et al., Journal of Reproduction and Development, December, 2007, found that CIDR with a timed AI protocol was especially ineffective at impregnating repeat breeder Holstein cows, from approximately 230 to 340 DIM, bred an average of 3.5 times previously; pregnancy rate was only 15%. This was despite the fact that the repeat breeders had normal estrous cycles and palpation and ultrasonography revealed no reproductive tract abnormalities. The Stevenson et al. paper points out that in previous studies, there has been a herd effect evident with CIDR; higher % pregnancy 28 d after AI using the Ovsynch protocol has been associated with CIDR in only approximately half of the herds studied, with no CIDR effect apparent in other herds.

Therefore Stevenson and colleagues elected to study the Ovsynch protocol with detection of noncycling cows, and addition of a progesterone CIDR for cows with no CL during the first 7 d of Ovsynch. The figure below is from their paper:

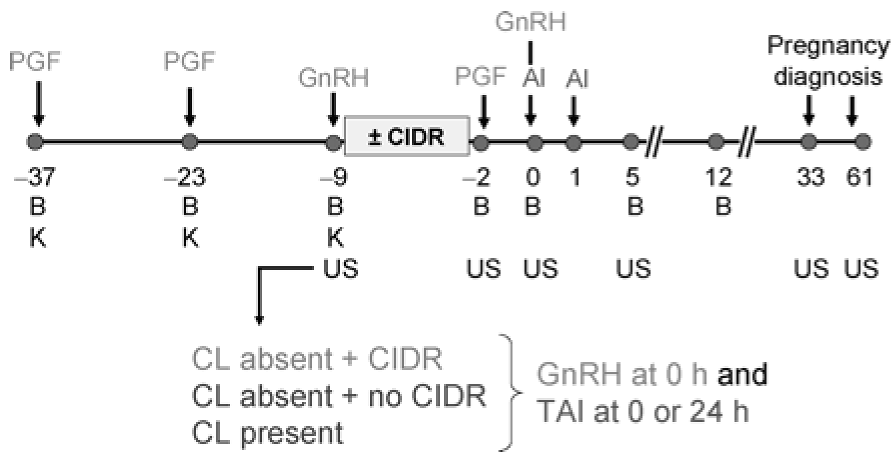

Figure 1. Experimental protocol showing the design of treatments. Heatmount detectors (K) were applied to detect whether a cow was mounted during a specific period. Activated heatmount detectors were replaced at each evaluation. Blood (B) was collected before various injections and twice post-AI. Presence of a corpus luteum (CL) was detected by transrectal ultrasonography (US) and cows without a CL alternately received a progesterone-releasing intravaginal controlled internal drug-release (CIDR) insert. Cows having a CL present received no CIDR insert. All cows received GnRH at 48 h after $PGF_{2\alpha}$ (PGF) and were inseminated before the second GnRH injection (0 h) or 24 h later within the 3 treatments. Pregnancy was diagnosed at 33 d after timed AI and was reconfirmed at 61 d after timed AI.

Below in Table 2 (table numbers are the same as in the original paper) are results among the 6 states in the study. I added bold type for some things I thought were of particular interest. There was considerable variation among locations; especially MN had poorer reproductive performance than the other states. Also, the % pregnancy loss from 33 d to 61 d after insemination was calculated in a way that makes the numerical values larger because it was a percentage of the pregnancies at 33 d that were later lost. E.g. KS, 42.9% - 37.3% = 5.6% of all potential pregnancies lost, but (5.6/42.9) = 12.9% loss of those pregnancies existing at 33 d. Therefore absolute differences in % pregnant between 33 d and 61 d ranging from 1.1% (WI) to 6.7% (MN) become 3.0% to 22.8%, respectively. The locations were actually 6 farms, one in each state, so this basically shows the herd effect. It is almost always true that management practices in dairy farming vary in effectiveness across herds and locations.

Table 2. Selected outcomes of lactating dairy cows enrolled at each location

	Location						
Item	IN	KS	MI	MN	MO	WI	Mean or total
Cows enrolled, n	80	217	153	194	242	186	1,072
DIM at first AI [1]	72[a]	79[b]	82[c]	69[d]	75[e]	72[a]	75**
% pregnant per AI at 33 d [2]	37.5	42.9	36.0	29.4	33.1	36.3	35.7
% pregnant per AI at 61 d [2]	37.5[a]	37.3[a]	33.3[ab]	**22.7[b]**	29.8[ab]	35.2[a]	32.0*
% preg loss (33 to 61 d) [2]	**0.0[ac]**	**12.9[a]**	**7.3[ac]**	**22.8[b]**	**10.0[ac]**	**3.0[c]**	**10.2***
% luteal activity before Tx [3]	92.5[ab]	91.2[a]	89.5[a]	**69.1[c]**	79.3[bd]	87.3[a]	83.7**
% regression of CL [4]	88.4[ab]	86.7[bc]	87.4[bc]	**81.9[b]**	94.8[a]	90.6[ac]	88.5**

[a–e] Location values having different superscript letters differ ($P \leq 0.05$).

[1]Standard deviation was 7.0.

[2]Determined by transrectal ultrasonography after the first postpartum AI.

[3]Based on progesterone concentrations measured in a total of 3 blood samples collected before each Presynch $PGF_{2\alpha}$ injection and before ultrasonography at the time of the first GnRH injection of the Ovsynch protocol. Cutoff values for luteal activity were based on progesterone ≥1 ng/mL and <1 ng/mL for no luteal activity.

[4]Cows having elevated (≥1 ng/mL) concentrations of progesterone at the $PGF_{2\alpha}$ injection of the Ovsynch protocol and low (<1 ng/mL) blood progesterone 48 h later.

**Location effect ($P < 0.01$);

*location effect ($P < 0.05$).

Below in Table 3 it can be seen that while presence of an ultrasound-detected CL was more likely among cows with serum progesterone > 3 ng/ml, more than half of cows with progesterone levels above 0.5 ng/ml had CL. Also, across all ranges of serum progesterone from 0.26 to > 6.0 ng/ml, 63% to 76% of cows had activated heat mount patches. The patches were expected to have detected prior estrus activity after the previous (second) injection of $PGF_{2\alpha}$. The authors stated, "presence of an activated heatmount detector had little relationship with the circulating concentrations of progesterone".

Because of the above results, I did an extensive literature search looking for research regarding whether heatmount detectors are associated with increased fertility, and found one paper by J Cavalieri et al. in the Australian Veterinary Journal, May 1995 suggesting that they are in heifers. There are a few reports that painting tailheads is equal to, inferior to, or better than heatmount detectors as far as detecting estrus; it certainly seems to me that many farms have gone back to painting tailheads instead of heatmount detectors. There is also evidence that heatmount detectors or painting tailheads increases estrus detection over visual observation alone. However, whether increased fertility which is really the goal, is being achieved by use of heatmount detectors has not been clearly demonstrated in older cows. The authors also mention that accuracy of painting ("chalking") tailheads for true estrus detection needs further study.

Table 3. Relationship between circulating progesterone concentrations in individual cows at the time of first GnRH injection of Ovsynch and the presence of an activated heatmount detector or an ultrasonically detected corpus luteum (CL) at the same time

Progesterone (ng/mL) at 1st GnRH injection	Cows with activated heatmount patches, %	Cows with ultrasound-detected CL, %
≤0.25	58.3 (98/168)	15.7 (24/153)
0.26 to 0.50	69.4 (43/62)	33.3 (21/63)
0.51 to 1.0	68.2 (45/66)	52.6 (30/57)
1.01 to 2.0	62.5 (60/96)	75.0 (69/92)
2.01 to 3.0	65.4 (71/107)	87.9 (87/99)
3.01 to 4.0	69.2 (117/169)	95.5 (148/155)
4.01 to 5.0	69.3 (104/150)	97.8 (135/138)
5.01 to 6.0	67.0 (59/88)	98.8 (79/80)
>6.0	76.2 (109/143)	97.7 (128/131)

There is considerable information in the original paper (again, JS Stevenson et al., Journal of Dairy Science, July 2008) about the accuracy of ultrasound and heatmount detectors when progesterone levels were used as the "gold standard" for diagnosing ovulation or noncyclicity. Briefly, one ultrasound examination before the first GnRH injection, 14 d after the 2nd $PGF_{2\alpha}$ injection (see Figure 1) correctly identified 13% of cows as noncycling (16% of cows were truly noncycling using standard of < 1 ng/ml progesterone) and 71% of cows as ovulatory (84% were truly ovulatory based on progesterone), for an overall accuracy of 84% and a positive predictive value (the % of cows called ovulatory by ultrasound that truly were ovulatory) of 95%. This was superior to heatmount detectors, with overall accuracy of 72% and positive predictive value of 86%. Accuracy of both methods varied among the 6 locations; ultrasound from 69% to 90%, heatmount detectors from 50% to 86%.

As far as the question of pregnancy loss and CIDR progesterone releasing devices, Table 6 below shows that among cows with no CL at first GnRH injection, there was increased % pregnant 33 d and 61 d after AI for CIDR treated cows. However, the loss of all potential pregnancies between 33 d and 61 d was 3.4% in "no CIDR" cows and 3.3% in CIDR treated cows, not different. Cows with a CL at first GnRH injection were also more likely to be pregnant at both time points; their loss of all potential pregnancies between 33 d and 61 d was 3.8%. There appears to be increased pregnancy among cows with a CL at first GnRH injection, and also for cows with no CL at that time if they are treated with a CIDR, compared to cows with neither a CL nor CIDR, during the first 33 d of gestation, but no apparent reduction in fetal losses from days 33 to 61. Once again, the benefit of CIDR varied among the 6 locations; 4 of the 6 locations accounted for the beneficial outcomes.

Table 6 also shows reduced ovulation in cows with no CL when CIDR treated (they become similar to cows with CL). This agrees with previous studies including by Rathbone et al. and Galvao et al. that CL or other progesterone sources have been associated with reduced ovulation, but not reduced pregnancy.

Table 6. Ovarian characteristics and fertility in response to presence or absence of a corpus luteum (CL) assessed by transrectal ultrasonography and progesterone treatment [controlled internal drug release (CIDR) insert] at the onset of the Ovsynch protocol

	CL absent[1]		
Item	No CIDR	CIDR	CL present[1]
Ovulation after first GnRH,[2] %	76.8^{a} (53/69)	47.1^{b} (49/104)	43.4^{b,x} (262/604)
Presence of CL at time of $PGF_{2\alpha}$,[2] %	76.8^{a} (53/69)	51.0^{b} (53/104)	95.7^{c,x} (584/610)
Diameter of ovulatory follicle at 2nd GnRH,[2] mm	16.7^{a} ± 0.4 (65)	16.2^{a} ± 0.4 (103)	15.2^{b,x} ± 0.1 (588)
Ovulation after second GnRH,[2] %	77.9 (53/68)	75.0 (78/104)	80.7 (488/605)
Pregnancies per AI at d 33, %	24.1^{a} (28/116)	32.3^{b} (50/155)	38.0^{b,x} (303/799)
Pregnancies per AI at d 61, %	20.7^{a} (24/116)	29.0^{b} (45/155)	34.2^{b,x} (273/799)
Pregnancy loss from d 33 to 61, %	14.3 (4/28)	10.0 (5/50)	9.9^{y} (30/303)

[a–c]Means having different superscript letters differ (*P* ≤0.05).

[x]Different (*P* ≤0.05) from cows with CL absent.

[y]Tended (*P* ≤0.10) to differ from cows with CL absent.

[1]Absence or presence of a CL as assessed by transrectal ultrasonography at the first GnRH injection of the Ovsynch protocol.

[2]Assessed at 3 of 6 locations.

The authors mention that this study did not agree with all previous studies of CIDR; results have varied just as they did among locations in this report. They also suggest further study is needed regarding the timing of CIDR inserts in the Ovsynch program. Taken together, the results of this interesting paper along with other studies add support to the concept that more bovine pregnancies could be maintained by progesterone supplementation in early gestation. Reversing the trend of recent decades that our cows are becoming deficient in progesterone may be a key to improving reproductive performance of dairy cows by reducing early embryonic losses. This appears to be an important subject for further investigation. As always I urge our readers to contact me, including suggestions for future topics of interest. I can be reached at (435) 797-1899 M-W, (435) 797-7120 Th-F or David.Wilson@usu.edu.

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