Prostaglandin Therapy and the Postpartum Cow

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Introduction

With the approval of PGF_2a [a] and its synthetic analog cloprostenol [b] (collectively PGF, hereafter) for use in lactating dairy cows, veterinarians have acquired a valuable tool for management of reproductive problems in these animals. To date, PGF has been used or advocated for nearly every conceivable reproductive disorder of cattle, from retained placenta to treatment for mismating. Some therapeutic uses are based on a recognized action of PGF, for example, luteolysis for treatment of unobserved estrus. Other uses are based on more speculative premises, for example, stimulation of the myometrium for treatment of postpartum metritis.

While the debate over the identity of the natural uterine luteolytic factor in the cow continues[1], there is no question that exogenous PGF is an effective lutelytic agent. The PGF products are therapeutic in any situation where termination of luteal function is indicated.

Therapeutic Considerations

Pyometra

Pyometra is the most common reproductive disorder in the early postpartum period of which PGF is an effective treatment. The classical bovine pyometra is an accumulation of pus in the uterus concurrent with persistence of the corpus luteum (CL). This results in anestrus. The appearance of a purulent exudate at the vulva is a common finding. The retention of the CL may be due to reduced luteolysin production by the endometrium, or an alteration of luteolysin secretion. Treatment of cows with PGF at the recommended luteolytic dose has resulted in a clinical recovery rate of greater than 90%[2,3]. In one trial[2], 65% of responding cows conceived after treatment. The luteolytic action of PGF is probably the basis for response in cows with pyometra.

Ovarian Cysts

Ovarian cysts are another postpartum reproductive disorder that may respond to PGF treatment. Three types of cystic ovarian structures have been described. The cystic corpus luteum is not regarded as a pathological state and may in fact be a normal stage in luteal development.[4] The follicular cyst and luteal cyst result from ovulation failure and are true pathological conditions. Luteal cysts have thicker walls than follicular cysts due to partial luteinization but the 2 types of cysts are difficult to differentiate by rectal palpation. In addition, it is possible to misdiagnose large, smooth-surfaced CL's as cystic structures. Keslar et al.[5] reported that cows diagnosed by rectal palpation as having ovarian cysts responded as well clinically to 25 mg of PGF_2a as to 100 ug of GnRH. Two of the 5 cows responding to PGF_2a had progesterone concentrations greater than 1 ng/ml while the other 3 were below 0.5 ng/ml. The 2 cows with higher progesterone may represent misdiagnoses of normal CL's, but not necessarily. They may also represent luteal cysts which responded to PGF_2a. No satisfactory explanation exists for the response of cystic cows with low progesterone concentrations. It is possible that exogenous PGF promotes gonadotropin release which would have a curative effect. The PGF_2a analog, alfaprostol [c] has been reported to induce cycling in anestrous mares[6] and this effect was attributed to gonadotropin release. Prostaglandin F_2a caused increased serum LH concentrations in the bull[7] and cow[8] but the effect in the cow was dependent on decreasing progesterone as occurs after luteolysis. No increase in LH was seen after cloprostenol treatment of heifers in estrus[9]. The increase in serum LH after PGF treatment of diestrous heifers was attributed to the removal of the negative feedback of progesterone after luteolysis and not to a direct effect of PGF on LH release[8,9]. The ability of a luteolytic dose of PGF to cause endogenous LH release in cystic cows has not been demonstrated.

Retained Placenta/Metritis

Recently there has been much interest in the use of PGF for the treatment of retained placenta and postpartum metritis in dairy cattle. Endogenous PGF_2a levels are elevated for 10 to 20 days postpartum in the normal cow[10] and the source of this prostaglandin appears to be the uterus[11]. Cows with more rapid postpartum uterine involution tend to have a longer duration of PGF_2a elevation[10,12]. Cows with longer PGF_2a elevations have a

[a] *Lutalyse, The Upjohn Co., Kalamazoo, MI 49001*
[b] *Estrumate, Haver, Shawnee, KS 66201.*
[c] *Alfavet, Hoffman-LaRoche Inc., Nutley, NJ 07110.*

tendency to resume normal estrous cycles sooner after calving as well[12]. The earlier onset of cyclicity results in more estrous periods before the time of breeding and this is associated with increased fertility in dairy cattle[13]. It is not illogical then to speculate that PGF treatment of postpartum cows may be beneficial.

Although there are several reports which support the use of PGF for promoting uterine involution and treating metritis, the mechanism for the therapeutic effect is unclear. Jackson[14] and Guay and Lamothe[15] attribute the therapeutic effect of cloprostenol in metritic cows to the luteolytic action of the drug. Cows with functional CL's returned to estrus and the normal uterine defense mechanisms active at this time are believed to be responsible for recovery. Etherington[16] reported that cloprostenol treatment of dairy cows on day 24 postpartum resulted in a decreased interval from calving to first observed estrus and conception. Again, this difference was attributed to the luteolytic property of the drug rather than a direct myometrial stimulation. On the other hand, Lindell and Kindahl[17] have reported that a luteolytic dose of PGF_2a given twice daily from day 3-13 postpartum accelerated the rate of uterine involution. In another report[18], fenprostalene[d] (a PGF $_2$a analog) administered one time to cows with retained placentas resulted in more and faster placental expulsions and a decreased incidence of metritis. These results would seem to be dependent on a uterotonic property of the drug used.

Steffan et al[19] reported that cows with metritis at 30 days postpartum responded as well to 2 injections of PGF_2a 14 days apart as to an intrauterine infusion of antibiotics. A beneficial effect was seen after PGF^2a in cycling and non-cycling cows and it was suggested that the response in non-cycling cows was due to a direct oxytocic action of PGF on the uterus.

There is ample evidence that PGF is uterotonic in the bovine[20 22], but the clinical significance of this effect is debated[22 23]. The short half-life of PGF_2a, along with the reported development of uterine refractoriness[22], would seem to limit its usefulness. Analogs of PGF_2a with longer half-lives may generate a more prolonged response but this has not yet been demonstrated. It should also be noted that the smooth muscle response to PGF_2a and its analogs is quite variable among species. Analogs developed for a specific luteolytic action in some species have been shown to be potent stimulators of uterine contraction in other species[24]. This variability makes it impossible to generalize about the uterotonic activity of the PGF products. Assessment of each product will be necessary before any therapeutic benefit can be claimed.

Unobserved Estrus

Treatment of unobserved estrus is the most common use for PGF in postpartum dairy cows. Zemjanis[25] has reported that 90% of anestrous cows are in fact cycling. Failure to observe these cows in estrus results in increased calving to first-service intervals as well as increased interservice intervals. Both situations lead to prolonged calving intervals. Cows that have entered the postpartum rebreeding period but have not been seen in estrus should be rectally palpated as part of a routine reproductive herd health program. Those with a mature CL are eligible for treatment with PGF. Bred cows found to be not pregnant at the time of pregnancy examination can be treated in a similar fashion. Cows treated in diestrus would be expected to undergo luteolysis in response to PGF and return to estrus sooner and more predictably than untreated cows.

The question of when to breed cows after PGF treatment for unobserved estrus still remains. Results obtained with single appointment inseminations generally are poorer than when cows are bred at estrus. Results with double appointment insemination at 72 and 96 hours are variable[26] but usually superior to a single appointment insemination. Although the best results may be expected when cows are bred at estrus after PGF, many times cows that respond to PGF are not detected in estrus and the treatment is wasted. Double-appointment AI will eliminate the problem of missed heats but it will result in some cows being bred at inappropriate times. Furthermore, cows which might otherwise have been seen in estrus and have required only 1 insemination will be bred twice. This is a particular concern where expensive semen is to be used. Many factors must be considered when selecting a breeding program for dairy cows treated with PGF. The farmer's ability to detect estrus is an important consideration. Appointment insemination may be more profitable in herds with low heat detection index. The age and lactation status play a role as well. Heifers and non-lactating adult cows return to estrus more rapidly after PGF treatment than do lactating cows[27 28]. The nutritional status will also affect the ability of cows to undergo normal estrus cycles and respond to PGF. Finally, the stage of the estrous cycle has a dramatic influence on the response of dairy cows to PGF.

The stage of the estrous cycle at the time of treatment affects dairy cattle breeding in several ways. First, variability in the interval to estrus in responsive cattle after treatment with PGF at different stages of diestrus has been reported.[27 29 30 34] In summary, cattle return to estrus sooner and more uniformly after treatment in early diestrus (days 7 and 8) than when treated in mid-diestrus (days 9-13). Different rates of luteolysis after treatment or differences in the follicular status at these respective stages of diestrus are two possible explanations for this response phenomenon. It is generally not possible to determine the stage of diestrus by rectal palpation so any variation in response due to cycle stage must be accommodated in the breeding recommendations. Generally, lacatating dairy cows treated at unknown stages of diestrus will return to estrus 2 to 7 days after treatment, making appointment AI a difficult

[d] *Bovilene, Diamond Laboratories, Inc., P.O. Box 863, Des Moines, Iowa 50304.*

proposition at best.

A second influence of the estrous cycle on PGF treatment is the variability of the rate of response after treatment. Several investigators have reported that cattle in early diestus (days 5-7) are less likely to respond to PGF than cattle in later diestrus.[28 31 35] In one study,[34] 25% and 66% of treated dairy cows responded to PGF treatment on days 6 and 7 of the cycle, respectively, while response rates were 90% or greater for each of days 8 through 21. Most reports indicate that the fertility of the estrus following successful PGF treatment in early diestrus is comparable to that following treatment in later diestrus.[27 28 31] Watts et al.[32], however, have reported that dairy heifers bred on the basis of estrus detection were less fertile after treatment in early diestrus (days 5 to 7) than in later diestrus (days 12 to 15). It should be noted that in general, fertility of cattle bred at estrus after PGF has been comparable to controls and in 2 recent reports,[36 37] an advantage of 10 percentage points in conception rate for PGF-induced estrus was found. Whether this represents a physiologic or managerial enhancement of fertility is unclear. At the very least, the fertility of the estrus after successful luteolysis with PGF is equivalent to that of a spontaneous estrus.

New Reproductive Management Methods for Dairy Herds Based on PGF

Estrous control schemes have been developed for breeding groups of cattle in restricted time periods. Variations of some of the programs can be used in dairy herds to increase the convenience of AI and possibly increase herd reproductive performance.[37 38] For dairy herds, these programs must continuously handle 1) new cows as they become ready for rebreeding after calving and 2) reintroduction of cows that have not conceived. An initial field test of a plan using cloprostenol on a weekly basis resulted in improved performance (reduced days to first service, reduced days open and improved conception rates) and showed the possibility that the estrous detection effort could be eliminated 2 or 3 days each week.[37] Based on these results, a weekly plan was developed using one PGF injection (day 2) per week for all cows needing insemination followed by a 4-day period for estrous detection and insemination on weekdays 4 through 7. No detection or insemination would be done on weekdays 1 through 3[38]. Preliminary results from a field evaluation of this program in 3 herds show reproductive performance equivalent to herdmate controls.

Another plan was developed in which breeding efforts are only needed for a 13-day period each 3 weeks.[38] Eight days into each 13-day breeding period, PGF is given to those cows still needing inseminaton. Both of these programs allow interservice intervals of approximately 21 days and utilize estrous detection skills on the farm. The weekly program would use more PGF than the 3-week program.

Estrous detection efforts can be completely eliminated in dairy herds by a "repeating double PGF injection with appointment AI" program.[38] Two major problems exist with this approach in lactating dairy cows. The conception rate achieved with this program in lactating dairy cows has been highly variable and frequently unexceptable. Also, pregnancy examination must be used to identify nonpregnant cows after insemination (since estrus detection has been eliminated) and this causes interservice intervals to 50 days or more. It seems unlikely that the labor saved would adequately offset the reduced reproductive performance and cost of PGF involved.

These programs show sufficient promise to be considered for inclusion in routine herd management, especially on farms with specific labor requirements and/or estrus detection problems.

Summary

The PGF products have become an established part of dairy practice. Although primarily used for their luteolytic properties, their potential for direct myometrial stimulation and gonadotropin release is now being explored. Further definition of these aspects of PGF is required before a therapeutic effect can be claimed. Successful use of PGF in AI programs requires an understanding of the variability in the estrous response after treatment. Cattle are less responsive to PGF in early diestrus than was previously believed. Additionally, the stage of diestrus at the time of treatment will influence the interval from treatment to estrus. Rectal palpation is not sufficiently exact to eliminate either of these variables. As a result, they must be accounted for in the breeding recommendations made to the client. At present, our recommendations for breeding lactating dairy cows after PGF treatment for unobserved estrus are as follows:

1. Observe treated cattle for estrus twice a day on days 2 to 7 after treatment. Breed 8 to 12 hours after the onset of standing estrus.

2. If appointment breeding is required, breed at 72 and 96 hours, or better, breed all cattle at 72 hours after treatment and observe for estrus twice a day on days 3 to 7 after treatment and rebreed if necessary.

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Questions & Answers:

Question: The effect of prostaglandin is sometimes affected by the dosage. I think it was given by one of the speakers but I never did hear the dose given.

Answer: Features of my talk were based on recommended luteolytic dose, that is the manufacturer's luteolytic dose, 25 mg PGF_2 500 micrograms of chloprostenol. There has been some concern that increasing or decreasing the dose will affect the response after treatment. The only reported evidence that I can recall seeing is an increase in the incidence of unobserved estrous in cows treated with less than the luteolytic dose of the product. Otherwise I have no specific information about the effective dose.

Question: I would like to address this question to Dr. Miller. What were your criteria for separating a mild metritis from a severe metritis? Did I understand you that your classification of severity was based on more than one treatment, or were there other factors that you considered in your classification?

Answer: The cows were classified by the cooperating veterinarian, and they were classified by him as to what he would call mild or severe. Then we took the mild group and randomly divided them into their treatment control groups. Sixty percent of those were treated, forty percent were not. Then we, of course, followed fertility. The severe we would have loved to not treated 40% of those, but we couldn't get them to let us do that. That was their decision, not ours. In other words, then we took the group that they gave us. We tried to use some way we could describe them. And the description I gave you I think pretty well fit. The exact description we used in the paper I can't recall. I think Dr. Darlington's description would reasonably well describe the difference between the two. I read the first one . . . "the description of the mild was cows with an enlarged cervix, and/or uterus, with or without pus, discharge, but no palpable pus in the uterus." Now I think for severe it would be an enlarged and/or cervix and uterus with palpable pus in the

uterus and with the pus discharge, either cheesy-white or bad odor.

Question: Question for Dr. Olson regarding the use in the intermediate postpartum period of gonadotropic releasing hormones. Do you vary the dose any, and what size dose were you using?

Answer: We were involved in one trial using gonatropin-releasing hormone in the intermediate postpartum period. Ours was a randomized trial where every other cow randomized got treated. Our parameters were fertility. We looked at interval from calving to conception and so forth. The ones that I'm really referring to, as far as the postpartum period, are a couple of papers out of European countries that have used it, and Wayne Eppington has used it as part of his thesis project. The dosages, as far as I know, were not varied on GnRH and the other comment again that I might bring forth would be that in Wayne's trial he had a fairly high number of cows that had retained fetal membranes and abnormal peripartum periods, and in turn he ended up with a very high incidence of pyometra in his cows that were treated with GnRH in that intermediate period. It seems like in one group 28% had pyometra.

Question: I'd like to ask Dr. Olson what length of time of milk withholding he is recommending using penicillin and oxytet intra-utero.

Answer: As far as penicillin, the easier thing is to comment about the test system which is bacillus thermanophilus, it is sensitive to .005 units of penicillin per ml. And if that test system is applied to cows that have received a million to a million and a half units of penicillin, there probably will be a detectable level of penicillin in the milk, the first one or two milkings after treatment and about 5% of the cows. In fact it would be about 4-5% on the first milking after treatment and less percentage after that. So I think most that I suggest is the level of penicillin in the milk is right at the level of sensitivity of the test system, and I think you have to then decide for yourself how to interpret that. I don't want to make that interpretation for you. Oxytetracycline, if you go at the high levels, according to the literature, 5 grams IU, the equivalent of a systemic dose, usually there are detectable levels in the milk the first one or two milkings afterwards. If you go with low levels, maybe the other way of looking at this, the test system, the bacillus thermonophilus system is looking a little bit like a goodnews—bad news joke. When they adapted the test system, changed it over to bacillus thermonophilus, it was 10 times more sensitive to penicillin than the previous test system. But as far as all other antibiotics, it is less sensitive. And I think with less than a gram level of tetracycline, it is very rare to find detectable residue in the milk.

Question: In regard to treatment of retained placenta, do you understand that use of oxytocin might give you a better uterus contraction than prostaglandin?

Answer: In the post partum cow, oxytocin was the more potent stimulator of uterine contractions, but these were normal postpartum cows. The other thing is, it has never really been conclusively demonstrated that lack of uterine contraction is responsible or associated with retained placenta. So it may be that prostaglandin, oxytocin, or ergonavine or whatever induce uterine contraction have absolutely no therapeutic benefit for retained placenta. But if you assume, that increased uterine contraction will be therapeutic, then I would guess that oxytocin would be a better way to go, because it has been demonstrated to be more potent, but I am not convinced that either one or any of them would be beneficial.

Question: Along those same lines, have any of you had a chance to evaluate or perhaps assess some of the data presented on some of the prostaglandin compounds with longer half lives in the immediate postpartum period for retained placenta.

Answer: I have not specifically worked with them. But even if you surmise that longer half lives will give you longer treatment exposure and potentially more uterine contractility there is also the problem that I reported of uterine refractoriness. If the uterus becomes less responsive to prostaglandin with repeated treatment, it may be also that it is less responsive to prostaglandin with one treatment with longer exposure. It may not necessarily give you more effective uterine contractions. But I can not specifically answer that question because we have not worked with the myometrial contractility problem with those drugs and I can't recall ever seeing a published report concerning that.

Question: I would like to address this question to Dr. Weaver. Monday in the advanced reproduction seminar, Dr. Ritt alluded to the fact that usually in first heat in these cows you generally have a smaller CL and lower progesterone level. Your data today showed that these cows that are in a negative energy balance, generally when you start to breed these cows, they have a lower blood progesterone and a lower CL. What I would really like to ask you is, what do you think, is this a cause or effect, this progesterone infertility? Do you think the fact these cows are negative energy balance longer causes them to act that cow that has her first heat, that she just has it later in her period, or do you think the level of progesterone itself has some effect on fertility and if so, do you think some of these normal infertile cows may have a lower progesterone level prior to heat?

Answer: I may need some help on this one from the panel. I think I recall one paper out of Japan where they looked at progesterone levels in the cycle preceding, I'm not sure whether there is nutritional data with it, but that suggestion was made that cows with higher fertility were simply those cows that had higher progesterone levels in that cycle. I still don't think that answers the question on cause and effect. Certainly there have been a number of studies that looked at fertility of high producing dairy cows, which would be more subject to being in negative energy balance and they have not been able to consistently demonstrate lower fertility on those cows.

Answer: There are a number, obviously, of nutritional relationships with fertility, and along the lines of energy, one that might come to mind, is the study with beef heifers that had different rations. But in essence the thrust of the project was whether the level of propionate in the diet was improved by feeding higher levels of grain or whether the level of propionate was improved by using Rumensin. The ultimate bottom line was that the animals were more fertile, and there has been some recent work to suggest that in turn the levels of propionate may be related to insulin and there has been work with animals that have been treated both with FSH and insulin in animals that were in such a negative state that normally you would not have had a response with FFH. If they were treated both with FSH and insulin, there was a very marked response to FSH through ovulation. So there is some work going on right on the cutting edge of how nutrition affects the reproductive physiology of the animal.

Answer: I just wanted to make a few comments about the relationships of the progesterone. No. 1, the early postpartum CL's, not a very robust one, in many instances gives you a short cycle so they would have low progesterone levels

relative to a normal life luteal function. A short cycle CL will not maintain sufficient period of time to initiate pregnancy recognition. So the embryo is destined not to be maintained. If we put that aside and then talk about the relationship of progesterone in a cycle prior to insemination related to fertility, it brings in a question about follicle dynamics and I think it is becoming quite interesting now that the quality of the follicle that grows in the pro-estrous period and ovulates and forms the corpus luteum has a lot to do with subsequent performance of that CL, and it may be that the CL prior to the estrous may be regulating to some degree follicular development, and you are getting a better quality follicle and a higher probability of conception, and there is some exciting work going on in that area at the present time. It is all interrelated to progesterone relationship, whether it be nutrition affecting that preovulatory follicle, the CL that regressed prior to the next estrous, or the effect of the CL in follicular development and this type of thing is all put together in controlling that relationship I think.

Question: Question to Dr. Olson regarding the diluent used for intrauterine infusions. Do you have any feelings whether that diluent should be saline or povidone solution, or whatever?

Answer: I probably don't have again good controlled studies to come to a real good, sound conclusion, but I think that if one goes through the literature and looks at some of the observations relative to irritants, that probably there is good reason to avoid putting something very irritating into a uterus at least that is already inflamed. My preference would be saline or providine. I think that propylene glycol is fairly irritating and I would tend to avoid that.

Question: I have a couple of questions for Dr. Olson. On the pyometra cow that you have to go back, say three weeks in a row and keep on repeating with prostaglandins before it is finally emptied out, why that happens, and the other one would be, a cow with a uterus that feels like a pyometra, but there is no palpable CL, how would you treat that?

Answer: As to the first, the treatment of pyometra with prostaglandin, I think that the overall response rate for a single treatment with prostaglandins is going to be in the range of 85-90%. One could then reason that still after two treatments there is still going to be a very small percentage that will have retention of fluid within the uterus. Within one of the projects we did do a cross over and we came back with estrogens for the third treatment and there weren't any cows left over that had not responded by the time two treatments with prostaglandins and with a cross over of estrogen. Regarding what to do with a cow without a palpable CL, I think you can look at it two ways. Often times, at least in terms of our palpation findings, and looking at the corresponding blood progesterone, it seems very often that the CL associated with retention of purulent exudate within the uterus is a rather small CL, and the probability is exceeding 95% of the time that there will be a CL there, at least by serum progesterone. I guess one could approach it from that way. The other if the ovaries are very small and you are convinced they aren't then the alternative would be to treat it as a uterine infection of the intermediate period, probably tetracyclines repeatedly.

Question: I have a question concerning the early metritis. What organism did you find in those? Was it *C. pyogenes* or some other organism?

Answer: There were a lot of bacteriological samplings that occurred in these cows. We looked at them in two different ways. We put the organisms that we found in the uterus in five different categories, and amongst those were all the coliforms and proteus, *C. pyogenes,* the gram negative anaerobes, *Clostridia,* and then grouped everything else as incidental bacteria. We looked at cows at least that had retained fetal membranes. They had lots of organisms, no matter which category, very early on, i.e. 100% of the cows that had retained fetal membranes had coliform organisms in the uterus. But in turn if we looked at these in terms of relative density of organisms, the coliforms were not all that high. The *C. pyogenes* built up rather rapidly. They started low, but they would build up rather rapidly through the postpartum period, and almost concurrently with the gram negative anaerobes. With *C. pyogenes,* whenever it was there it was there in relatively high numbers, compared or in contrast to the coliforms. I think that early on, the organisms that we would be very concerned about would be clostridiums as a category of organisms in the very early postpartum period and probably having a significant role with other gram negative anaerobes in the very early postpartum infections.

Panel Member: Since we still have time, and no one else is asking any questions, I wonder if I could make a couple of comments.

I think from Dr. Millers work in particular, the John Doe herd that he flashed the results up, illustrates the point I was making on Monday about the impact that you can have by alternating management perhaps rather than treating some conditions. You know the relative impact of say, treating metritis versus altering herd management. The obvious thing that happened in the John Doe herd was heat detection improved, with a shorter calving to first breeding interval, and then the improvement in the ratio of single to double estrous cycles had a dramatic impact on calving intervals, the number of cows left open, and all the rest. And I think that everyone who saw that slide should really take that message from it. I wanted to emphasize that. In relation to the ratio of single to double interestrous intervals, in fact what I said was the ratio should be better than 1:6, which means that it should be 1:7, which is exactly what Leon said, and so that is fine. And then when I looked at the range of days that you were unsure Dr. Miller it is one day off from mine, I use 8 into 24 as a ratio of 39 to 45 day heats, and you use 39 to 46, at least that's what you get in the slide. There you get 1:8, I suppose and so we'll agree. So we won't have any argument on that one. Then looking at the nutrition story, certainly Dr. Trevor McClure at the University of Sidney did a lot of work looking at blood glucose levels both in cows that were in different feeding situations, and then experimentally by including hypoglycemia through insulin treatment, and demonstrated a significant effect on conception rate. Now I don't think he explained the mechanisms, but he hypothesized some, including both the hypothalamus and pituitary, and also maybe some ovarian response. I was trying to think of what work it was, but there is some U. S. work that demonstrates some effect of glucose in the animal on varying activity, and I think it might have been Hansel's work. The other thing relating to the effect of progesterone on subsequent fertility. I know I can think of three papers but I can't name chapter and verse in either but it looked at progesterone levels and subsequent heat expression. I think there alone we may have a good explanation why fertility might be higher with heats following high level progesterone cycles, simply because the expression of heat is improved in later cycles and so the cows are inseminated at a more appropriate time and achieve higher conception rates.