THE EFFECT OF PROSTAGLANDIN INHIBITOR ON PREGNANCY RATES OF HEIFER EMBRYO TRANSFER RECIPIENTS

By

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GRADUATE COMMITTEE APPROVAL

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ABSTRACT

THE EFFECT OF PROSTAGLANDIN INHIBITOR ON PREGNANCY RATES OF HEIFER EMBRYO TRANSFER RECIPIENTS

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Department of Plant & Animal Science

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Manipulation of the reproductive tract results in increased levels of prostaglandin, which may, in turn, reduce pregnancy rates in embryo recipients. Administration of a prostaglandin inhibitor prior to embryo transfer improves pregnancy rates in cows. Embryo transfer into heifers is more difficult and often requires additional manipulation of the uterus. This study was designed to determine whether administration of the prostaglandin inhibitor, flunixin meglumine, immediately prior to embryo transfer increases pregnancy rates in heifers. Heifers (n=466) were divided into two equal groups based on BCS (range=6-7) and weight (range=256-455). Estrus was synchronized in heifers by giving two injections of prostaglandin $F_{2"}$ (PGF) eleven days apart with a two day stagger between groups. Heifers in each group were watched for estrus for four days following the second PGF injection. Each heifer detected in estrus (n~389; 83%) was palpated seven days later for the presence and location of an acceptable corpus luteum;

development of the reproductive tract (uterine tract score; 1=prepubertal, 5=mature tract) and amount of uterine tone (uterine tone score; l=high tone, 2=medium tone, 3=low tone) were also estimated. The 352 heifers that had an acceptable CL were paired based on day of detected estrus, body condition score, body weight, and uterine tone score. One heifer of each pair was randomly assigned to receive 10ml of flunixin meglumine (IM) just prior to embryo transfer. Time between injection until completion of embryo transfer ranged from 2-25 minutes. All heifers received a single frozen/thawed embryo transferred by one of two experienced technicians. Data collected at the time of transfer included cervix score (1-3; 1=easily penetrated, 3=difficult), ease of transfer score (1-3; l=gun easily manipulated to site of transfer, 3=difficult), embryo placement in the uterine horn (U=upper 1/3, M=middle 1/3, L=lower 1/3), and technician. Pregnancy results were obtained 90 days after transfer via rectal palpation. The logistics procedures and chi-square analysis of SAS were used for data analysis.

Pregnancy rates did not differ (P>0.05) between heifers receiving prostaglandin inhibitor (81/161; 50%) versus heifers receiving none (75/165; 45%). Body condition score (BCS), body weight, cervix score, ease of transfer, embryo placement, or transfer time neither differed between treatment groups (P>0.05) nor had any effect on pregnancy rates following embryo transfer (P>0.05). In conclusion, the administration of a prostaglandin synthesis inhibitor prior to embryo transfer will not increase the rate of pregnancy establishment in beef heifers under the conditions utilized in this experiment.

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I wish to thank my family for their willingness to be uprooted and moved from place to place. Jana, my devoted wife, has sacrificed a great deal. She has provided tremendous support, encouragement and patience. Without her this project would never have been realized.

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The Effect of Prostaglandin Inhibitor on Pregnancy Rates of Heifer Embryo Transfer Recipients

A Manuscript prepared for submission to
Theriogenology

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ABSTRACT

Manipulation of the reproductive tract results in increased levels of prostaglandin $F_{2\alpha}$ (PGF) within the uterine lumen and circulatory system, which may, in turn, reduce pregnancy rates. There is evidence that administration of a prostaglandin inhibitor prior to embryo transfer may improve pregnancy rates in cows. Embryo transfer into heifers is more difficult and often requires additional manipulation of the reproductive tract. This study was designed to determine whether administration of the prostaglandin inhibitor, flunixin meglumine, immediately prior to embryo transfer increases pregnancy rates in heifers. Heifers (n=466) were divided into two equal groups based on BCS (range=6-7) and weight (range=256-455 kg). Estrus in heifers was synchronized by giving two injections of PGF eleven days apart. There was a two day stagger in injection times between the two groups. Heifers were watched for estrus for four days following the second PGF injection. Those detected in estrus during the four-day period were considered synchronized and utilized for further experimentation. Synchronized heifers (n~389; 83% synchrony) were palpated 7 days after estrus detection for the presence and location of an acceptable corpus luteum; amount of uterine tone was also estimated (uterine tone score; l=high tone, 2=medium tone, 3=low tone). The 352 heifers that had an acceptable CL (90% utilization rate) were paired based on body condition score, body weight, and uterine tone score. One heifer of each pair was randomly assigned to receive 10ml of flunixin meglumine (IM) just prior to embryo transfer. All heifers received a single frozen/thawed embryo transferred by one of two experienced technicians. Time from injection until completion of the transfer ranged from 2-25 minutes. Data collected at the time of transfer included cervix score (1-3; 1=easily penetrated, 3=difficult), ease

of transfer score (1-3; l=gun easily manipulated to site of transfer, 3=difficult), embryo placement in horn (U=upper 1/3, M=middle 1/3, L=lower 1/3), injection time, implant time, and technician. Pregnancy results were obtained 90 days after transfer via rectal palpation. The logistics procedures and chi-square analysis of SAS were used for data analysis.

Pregnancy rates did not differ (P>0.05) between heifers receiving prostaglandin inhibitor (81/161; 50%) versus heifers receiving none (75/165; 45%). Body condition score (BCS), body weight, cervix score, ease of transfer, embryo placement, or transfer time neither differed between treatments (P>0.05) nor had any effect on pregnancy rates following embryo transfer (P>0.05). In conclusion, the administration of prostaglandin inhibitor prior to embryo transfer did not increase the rate of pregnancy establishment in beef heifers.

INTRODUCTION

Embryo transfer in cattle has become commonplace throughout much of the world. However, in spite of increased utilization of this technology, establishment of pregnancy in recipient cattle remains highly variable. This variation may be a result of embryonic, maternal or environmental factors or a combination of any of these factors (Sreenan and Diskin, 1987).

Successful pregnancy establishment is dependent upon the presence of a viable embryo in the uterine horn ipsilateral to a functional corpus luteum prior to the time of maternal recognition of pregnancy. The vast majority of embryo transfer occurs 6-7 days after a recipient cow has been detected in estrus. Typically, rectal palpation of the ovaries to detect the presence and quality of a corpus luteum is followed by manipulation

of the cervix and uterus to facilitate penetration of an embryo-bearing catheter into the lumen of a uterine horn ipsilateral to the corpus luteum. Placement of the catheter and deposition of the embryo as far as possible up the uterine horn appears to maximize pregnancy rate. However, placement of the catheter through the cervical lumen, into the uterus, and up the uterine horn can be very challenging in some cattle.

Pregnancy rates may be compromised in some embryo recipient cattle because manipulation of the uterus elevates levels of prostaglandin $F_{2\alpha}$ (PGF) in blood (Schallenberger, Odensvik). Indeed, even minor manipulation of the cervix may lead to increased PGF in the lumen of the uterus (Wann). Increased PGF in the uterine lumen may interfere with embryonic development and affect embryo quality directly (Scenna et al, 2004). Alternatively, increased PGF in blood may indirectly affect pregnancy establishment by compromising luteal function (Beal, 1996).

Administration of ibuprofen lysinate, an inhibitor of prostaglandin synthesis, to embryo recipient dairy heifers 1 hour before embryo transfer increased pregnancy rates by 26% (Elli et al, 2001). In a setting where large scale embryo transfer takes place under adverse environmental conditions, a one hour wait after treatment, before transfer is unacceptable. This experiment was designed to determine whether or not administration of the PG inhibitor, FM, immediately prior to embryo transfer, would lead to higher pregnancy rates in recipient beef heifers.

MATERIALS AND METHODS

This experiment utilized Hereford, Murray Gray, and Hereford-Angus crossbred heifers approximately 16 months of age located in New South Wales, Australia, (n=466).

Estrus was synchronized in heifers by giving two injections of 25mg dinoprost tromethamine (Lutalyse^{R}, Pharmacia Ltd., Rydalmere, NSW Australia) eleven days apart. A KMAR patch was glued to the tail head of each heifer; activation was interpreted as evidence of estrus. The heifers were run through an alleyway once a day to visualize KMAR activation; heifers with activated KMARs were sorted into a separate paddock. Seven days after detected estrus, each heifer observed in estrus (n=389; 83%) was weighed, given a body condition score (1-9, Battaglia), and palpated to determine the presence and location of an acceptable corpus luteum. The reproductive tract was also palpated and a tract maturity score (based on the diameter of the horn at the bifurcation in millimeters; 1=>20mm; 2=20-25mm; 3=<25mm; Veserat) and uterine tone score (1=high tone; 2=medium tone; 3=low tone) was given. The presence or absence of a luteal cavity and whether or the not the CL was imbedded in the ovary was also noted. The 352 heifers (90% of those detected in estrus) that had acceptable CL were paired based on body condition score, body weight, and uterine tone score. One heifer in each pair was randomly assigned to receive 10mL of 50g/mL FM (Fluximine^{R}, Bomack Laboratories Ltd., Manukau City, Auckland New Zealand). All recipients received 0.5 mL of acepromazine immediately prior to transfer. Transfers were performed by one of two experienced technicians. All heifers received a single frozen/thawed embryo. Data collected at the time of transfer included cervix score (1-3; 1=easily penetrated, 3=difficult), ease of transfer score (1-3; l=gun easily manipulated to the site of transfer, 3=difficult), location of embryo placement in uterine horn (U=upper 1/3, M=middle 1/3, L=lower 1/3), injection time, transfer time, and technician. Pregnancy results were obtained 90 days after transfer via rectal palpation. Twenty six recipient heifers that had

missing data points were eliminated from the analysis. The logistics and chi-square analysis procedures of SAS were used to perform data analysis.

RESULTS

Body weight, body condition, uterine tone, cervix, ease of transfer, placement, and elapsed time scores (time from FM injection until completion of the transfer; range= 2-25 minutes) did not differ between treatments (Table 1). Overall pregnancy rates, as determined by chi-square analysis, did not differ ($P>0.05$) between treatments (FM= 81/161; 50% versus control= 75/165; 45%, Figure 1). Pregnancy rate was not affected by body condition score (Table 2), uterine tone score (Table 3), ease of transfer score (Table 4), location of embryo deposition (Table 5), condition of the corpus luteum (Table 6), or corpus luteum location (Table 7).

DISCUSSION

The overall pregnancy rate in this field study was 48%. This pregnancy rate is reasonable when compared with other studies using frozen-thawed embryos in heifer recipients (Hasler, 2001).

Elevated levels of prostaglandin $F_{2\alpha}$ in the uterine lumen may be responsible for early embryonic loss in cycling cattle (Scenna et al, 2004). Manipulation of the uterus or cervix induces the release of PGF into the uterine lumen and the blood stream. Although not monitored in this study, there is preliminary evidence supporting the idea that manipulation of the cervix and uterus when performing embryo transfer does induce the release of PGF from the uterus (Schrick et al, 2000). Others, however, have not seen an

increase in circulating levels of PGF as measured by the level of its metabolite (Odensvik et al, 1993).

An increase in luminal levels of PGF could increase embryonic mortality. There is evidence that PGF may act directly on pre-compacted and compacted embryos by interfering with subsequent development and viability (Scenna et al, 2004). Indeed, administration of PGF to progestogen-supplemented, inseminated cows five to eight days after insemination resulted in embryos that were developmentally retarded and which had decreased embryo quality scores as compared to embryos from saline-treated cows (Hockett et al, 2004).

Administration of a large dose of PGF on days 5-16 of the estrous cycle can induce complete luteolysis in cattle (Beal, 1996). The luteolytic effect of a luminal increase in endogenous PGF has not been evaluated thoroughly (Odensvik et al, 1993) but luminal administration of exogenous PGF can induce luteolysis in cyclic cattle . Whether cervical and uterine manipulation, similar to that which occurs during embryo transfer, can induce luteolysis in cyclic heifers awaits further investigation.

Administration of ibuprofen lysinate, which prevents the formation of prostaglandin by inhibiting cyclooxygenase, one hour prior to transfer resulted in an increased pregnancy rate in dairy heifers that received frozen-thawed embryos (Elli et al, 2001). There is also preliminary evidence that FM, given immediately before ET, improved pregnancy rates in embryo recipient cows (Schrick et al., 2000). This study examined the effects of FM given to beef heifers immediately prior to ET on pregnancy rates at 90 days of gestation. Administration of the inhibitor, at a dosage rate shown to be efficacious in cows (Schrick et al., 2000), did not improve the pregnancy rate in heifers. It is possible that cervical and

uterine manipulation in these heifers did not result in significant production or release of PGF from the reproductive tract. The vast majority of the embryos were reported as being very easily transferred into the upper third of the uterine horn. Interestingly, this is the preferred site of deposition since pregnancy rates are highest when embryos are transferred here (Beal et al., 1998). However, this should potentially cause the greatest amount of PGF release since nearly the whole uterine horn is manipulated. It remains to be determined if manipulation of the cervix or of the uterus or of both causes maximal PGF release.

The time from injection of FM until completion of the transfer, which included moving the animal from the injection chute into a chute used for transfer, ranged from 2-25 minutes, with the vast majority having an elapsed time of less than five minutes. The use of experienced personnel affected the ease of transfer and potentially could have impacted the amount of uterine PGF release induced by the manipulation. The effect of the degree of cervical/uterine manipulation on PGF release is unknown.

The experience level and time to perform the transfer was not reported in the study where treatment with ibuprofen lysinate resulted in an increased pregnancy rate in recipient dairy heifers (Elli et al, 2001). However, both the inhibitor utilized, the timing of administration, and the breed of cattle used differed between that study and ours. It may be that ibuprofen lysinate is more effective than flunixin meglumine in inhibiting uterine PGF synthesis and release. Alternatively, administration of the inhibitor one hour before transfer may have given the inhibitor time to travel to the uterus, thereby increasing its efficacy in inhibiting release. Treatment with an inhibitor just prior to transfer would make utilization more attractive in large scale embryo transfer operations. It remains to

be determined if ibuprofen lysinate will be effective in improving pregnancy rates when administered during this time frame. A difference in results due to the breed of cattle utilized can not be overlooked and awaits additional study.

In conclusion, the administration of the prostaglandin synthesis inhibitor flunixin meglamine immediately prior to embryo transfer in beef heifers did not alter overall pregnancy rates. Therefore, administration of a prostaglandin inhibitor to embryo recipient heifers immediately before transfer can not be recommended.

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LEGEND TO FIGURES

FIGURE 1. Pregnancy rates of control heifers or heifers receiving flunixin meglumine (500mg) just prior to embryo transfer.

TABLE 1. Body weight, body condition, and reproductive tract scores (SE) of control heifers or heifers treated with flunixin meglumine (500mg) just prior to embryo transfer.

TABLE 2. The effect of body condition score on pregnancy rate in embryo recipient heifers.

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TABLE 4. The effect of ease of transfer in the uterus on pregnancy rate in embryo recipient heifers.

TABLE 5. The effect of location of embryo deposition in the uterus on pregnancy rate in embryo recipient heifers.

TABLE 6. The effect of condition of the corpus luteum on pregnancy rate in embryo recipient heifers.

TABLE 7. The effect of location of the corpus luteum on pregnancy rate in embryo recipient heifers.

FIGURE 1

Pregnancy rates of control heifers and heifers receiving flunixin meglumine (500mg) just prior to embryo transfer.

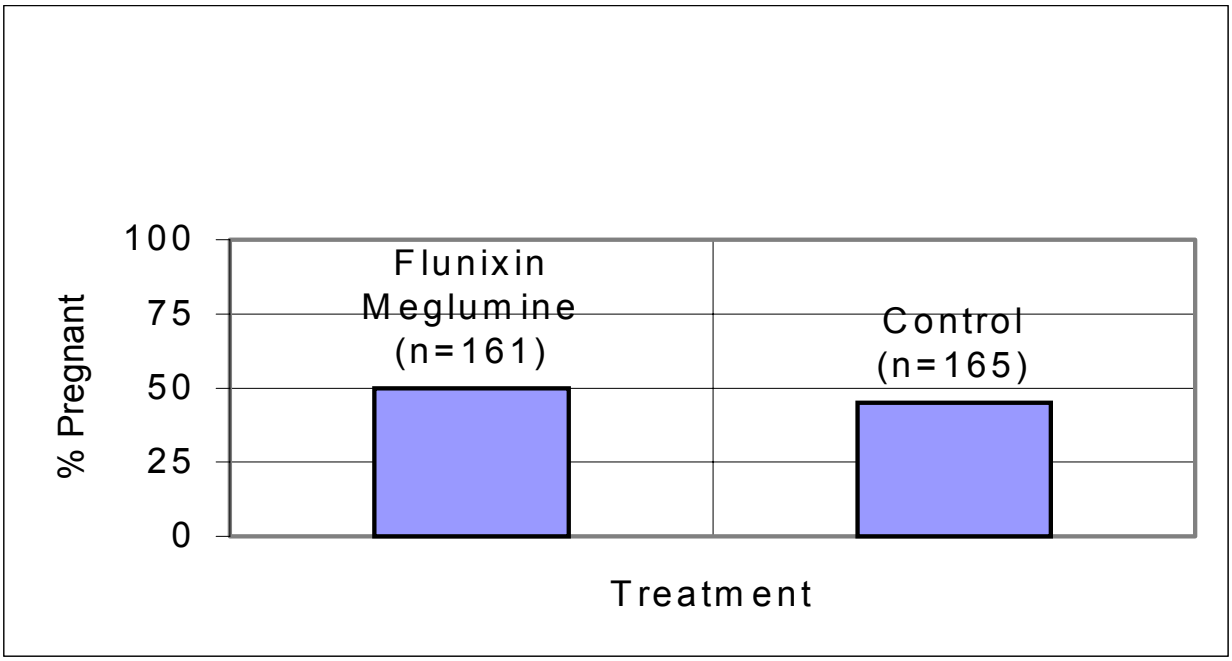

TABLE 1

Body weight, body condition, and reproductive tract scores (SE) of control heifers and heifers treated with flunixin meglumine (FM) (500mg) just prior to embryo transfer.

	Determined prior to transfer			Determined at time of transfer			
	Body Weight (kg)	Body Condition Score[1]	Uterine Tone Score[2]	Cervix Score[3]	Ease of Transfer Score[4]	Placement Score[5]	Elapsed Time (min)
FM	361(3)	6.1(.1)	2.2(.1)	1.3(.1)	1.2(.1)	2.8(.1)	5.0(.3)
Control	359(2)	6.1(.1)	2.3(.1)	1.4(.1)	1.3(.1)	2.8(.1)	5.5(.4)

[1]Body condition score on a scale of 1-9; 1=emaciated, 9=extremely obese.

[2]Uterine tone score on a scale of 1-3; 1=flaccid, 3=rigor.

[3]Cervix score based on ease of penetration of transfer rod on a scale of 1-3; 1=easy, 3=difficult.

[4]Score based on ease of penetration of transfer rod in the uterus on a scale of 1-3; 1=easy, 3=difficult.

[5]Placement score based on location of transfer in uterine horn on a scale of 1-3; 1=lower 1/3, 2=middle 1/3, 3=upper 1/3.

TABLE 2

The effect of body condition score on pregnancy rate in embryo recipient heifers.

	Body Condition Score	
	6	7
Percent Pregnant	49	48
(number pregnant/number of recipients)	(151/311)	(13/27)

TABLE 3

The effect of uterine tone score on pregnancy rate in embryo recipient heifers.

	Uterine Tone		
	Low	Medium	High
Percent Pregnant	33	49	50
(number pregnant/number of recipients)	(7/21)	(102/207)	(56/111)

TABLE 4

The effect of ease of transfer in the uterus on pregnancy rate in embryo recipient heifers.

	Ease of Transfer Score		
	1	2	3
Percent Pregnant	49	44	63
(number pregnant/number of recipients)	(123/251)	(27/61)	(5/8)

TABLE 5

The effect of location of embryo deposition in the uterus on pregnancy rate in embryo recipient heifers.

	Location in Uterus	
	Middle Third	Upper Third
Percent Pregnant	43	50
(number pregnant/number of recipients)	(29/68)	(123/247)

TABLE 6

The effect of condition of the corpus luteum on pregnancy rate in embryo recipient heifers.

	Condition of the Corpus Luteum		
	Good, Palpable	Small	Embedded
Percent Pregnant	47	65	35
(number pregnant/number of recipients)	(134/284)	(11/17)	(6/17)

TABLE 7

The effect of location of the corpus luteum on pregnancy rate in embryo recipient heifers.

	Location of Corpus Luteum	
	Right Ovary	Left Ovary
Percent Pregnant	51	44
(number pregnant/number of recipients)	(84/165)	(68/154)

LITERATURE REVIEW

INTRODUCTION

Embryo transfer in the bovine has potential to be a very effective tool in the quest to improve herd genetics economics in cattle production. Some dairymen and few beef producers have used ET at one time or another with widely varying levels of success and/or failure.

There have been and continue to be numerous studies dedicated to finding ways to improve the success rates of ET. As a result, the ET industry has made improvements in procedures that have resulted in increased pregnancy rates. However, in order for the industry to continue to grow, success rates need to be improved and be more consistent.

Not all the pressure to improve the industry can or should be placed on the shoulders of the ET technician's skills and methods alone. Both embryo viability and the ability of the recipient to carry a pregnancy to term affect the final outcome of ET.

Recipient's Role

Statistical modeling has recently been used to estimate the contribution of the embryo and of the recipient to pregnancy success. Using 7 different data sets to evaluate the model, the author concluded that both the recipient and the embryo play critical roles (McMillan, 1998). The fertility of the recipient is affected by factors such as body condition, nutrition, age, and site of embryo deposition, heat stress, and prostaglandin $F_{2\alpha}$.

NUTRITION AND BODY CONDITION SCORE

Nutrition is one of the most critical factors affecting reproductive performance (Short and Adams, 1988). Body condition score (BCS), a subjective evaluation of the amount of fat present in the animal, is a reflection of nutritional status. Heifers in good body condition, on an adequate plane of nutrition, and with a history of normal cycles are preferred embryo recipients (Sreenan and Diskin, 1987). Improved feeding of poor conditioned (BCS 1-3) heifers will increase pregnancy rates (Leaver, 1977). On the other hand, providing excess feed to cattle in good (BCS 6-7) or obese (BCS 8-9) condition will depress pregnancy rates (Ducker et al. 1985). Thus, the goal should be to use reproductively sound heifers in moderate body condition (BCS 4-5) and on a level plane of nutrition.

Recipient body condition at the time of transfer affects the outcome. In dairy cattle a 37% increase in pregnancy accompanied a whole unit increase in body condition score (Ambrose et al., 1999).

Dairy cattle in a negative energy balance have higher levels of uterine $PGF_{2\alpha}$ and an increase in the sensitivity of the uterus to release $PGF_{2\alpha}$ (Butler, 1998). Since $PGF_{2\alpha}$ can cause luteolysis which results in an aborted pregnancy, it is important to avoid a negative energy balance. In addition, a decreased availability of energy in heifers leads to a lack of cyclicity and impaired fertility. Thus, adequate nutrition levels for recipients are vital to success in ET.

AGE

The age of the recipient plays a major role in the success rates of an embryo transfer program. However, an animals size and weight should ultimately determine the suitability of a recipient. Some managers use a minimum weight range to decide whether or not a heifer is mature enough to receive an embryo. In general, a weight limit is a good indicator of heifer reproductive tract maturity and cyclicity (Dahlen et al., 2003). The pregnancy rates of recipient heifers are higher when the heifers are over fifteen months of age when compared to heifers under fifteen months, 76.1% and 66.7% respectively (Lee, 1988).

SITE OF EMBRYO DEPOSITION

There has been some controversy over where the embryo should be deposited in the uterine horn. The embryo should be placed in the horn ipsilateral to the functional corpus luteum. Placing the embryo ipsilateral to the corpus luteum will result in significantly higher pregnancy rates (Siedel, 1980, Tervit et al., 1997). In addition, if transfers occur ipsilateral to the CL there is no difference in pregnancy rates due to the side of the uterus (left versus right) to which embryos transferred (Hasler et al., 1987).

Controversy arises over how far up the uterine horn the embryo should be placed. Few studies have been performed in this specific area; however, one study compared deep placement (two thirds up from the external bifurcation) to shallow placement

(adjacent to the external bifurcation). Pregnancy rates are higher when the embryo is placed far up the uterine horn rather than shallow (65.9% to 29.6%; Beal et al., 1998).

HEAT STRESS

There has been little research done relative to effects of stress on embryo transfer recipients. One possible reason for this is that stress is a very difficult thing to measure and compare accurately. Another difficulty associated with stress is that it may be expressed as a result of a variety of different circumstances such as excessive loud noises, unfamiliar surroundings, over crowding, extreme temperatures, and so forth. Of the many possible causes of stress, temperature seems to be one of the few that have been quantified and studied.

Heat stress may significantly affect cattle reproduction in three ways. First, it is more challenging to detect estrus in cattle when they are subjected to heat stress. Heat stressed cattle expressed estrus for 4.5 hrs less than non-stressed cattle (Abilay et al., 1975). In addition, the frequency of mounting decreases during the hotter months of the year by nearly half (Nebel et al., 1997). One likely reason for the decreased expression of estrus is physical lethargy experienced by heat stressed cattle. Another possible reason for decreased estrus expression could be of hormonal origin. Heat stressed animals have less circulating estradiol-17β concentrations, and in some cases have high adrenocorticotropin levels which can inhibit estradiol-induced behavior (Hansen and Arichega, 1999).

The second way that heat stress may affect reproduction is by reducing conception rates. The decrease in conception rates may be the result of temperature

variations in and/or reduced blood flow to the reproductive tract (Thatcher et al., 1986). As a result of the temperature and blood variations in utero, the probability of early embryonic death would increase (Thatcher et al., 1986).

The third way that heat stress adversely affects reproduction is in elevated levels of $PGF_{2\alpha}$. Beef and dairy cows have increased plasma concentration of $PGF_{2\alpha}$ while experiencing heat stress (Malayer et al., 1990). High levels of $PGF_{2\alpha}$ have a detrimental effect on developing embryos (Schrick et al. 1993).

PGF EFFECTS ON EMBRYO RECIPIENTS

PGF plays a delicate role in embryo transfer recipients. Maintaining a unique balance of PGF is necessary to achieve optimum pregnancy rates. Because PGF stimulates endometrial vascularity, blastocyst hatching, and embryo implantation (van der Weiden et al. 1993; Dinchuck et al. 1995; Psychoyoset et al. 1995; Charpigny et al. 1997; Lim et al. 1997, Reese et al. 1999) it is important that its effects are not totally removed. On the other hand, too much PGF may cause premature luteolysis or be embryo toxic (Seals et al. 1998).

Naturally then, the goal is to control the release of PGF so that its actions will benefit rather than compromise a pregnancy. Therefore, the dose of the PGF inhibitor may be crucial to optimizing pregnancy rates. Too high a dose may cause the negative effects mentioned above, while too little a dose may have no effect at all. In a study performed by Elli et al. 2001, treatment animals were given a dose of ibuprofen that was specifically designed to decrease but not abolish the production of PGF compounds.

PGF EFFECTS ON EMBRYOS

Embryo viability is detrimentally affected by exposure to high levels of PGF. For example, postpartum cows have a higher concentration of uterine PGF levels than normally cycling cows, as a result the embryos from cattle with high PGF levels were of lesser quality. Because of these findings PGF is thought to decrease embryonic survival in postpartum cows (Schrick et al. 1993).

Embryos exposed to PGF during early development become arrested at the morula stage of development. Embryos may be particularly sensitive to the embryotoxic effects of PGF (Scenna et al, 2004; Fazio and Schrick, 1997; Herandez-Fonseca et al. 1997). Further research by Hockett et al. (2004) re-emphasized this phenomenon. His results showed that cows treated with PGF produced 64% embryos in the morula stage while the control group produced none, suggesting that PGF inhibits development beyond the morula stage. In addition, the quality of recovered embryos from the PGF treated cows were much lower than the control group. A study performed on cows supported these findings and showed that even when cows were supplemented with exogenous progesterone and subsequently exposed to PGF that embryo development was inhibited (Hockett et al, 2004).

Research involving other species of animals has resulted in similar results. Studies including rabbits (Maurer and Beier, 1976) and rats (Breuel et al. 1993a) both showed that PGF had an inhibitory effect on the development of embryos, however caution was emphasized in drawing comparisons among the species due to differences in embryonic development.

Exactly how PGF inhibits embryo development is not known. It is possible that PGF binds a receptor that leads to an increase in intracellular Ca which disrupts the normal compaction process. It is also possible that PGF diffuses across cell membranes and alters intracellular concentrations , thus disrupting the normal compaction process. Either way, PGF seems to prevent the normal compaction process which leads to poorly developed embryos.

EFFECTS OF PGF SYNTHESIS INHIBITORS

As a result of the negative effects of PGF on embryos, it follows that inhibiting PGF production may lead to an increase in pregnancy rates. Two drugs have been studied to determine their effectiveness in improving pregnancy rates in cattle via PGF inhibition. Banamine, an endoperoxide synthase inhibitor, has been used to prevent the release of PGF. One study showed that when 10 ml banamine was administered intramuscularly during the embryo transfer there was a 16% improvement in pregnancy rates (Schrick et al. 2000). However, other studies performed have not shown such dramatic results.

Another drug that has been used to inhibit PGF release is ibuprofen. Ibuprofen, among other things, prevents the formation of prostaglandins by inhibiting cyclooxygenase activity. In a study involving women undergoing IVF, a daily dose of 100mg of asprin significantly increased their pregnancy rates when compared to non-treated women (Rubinstein et al. 1999). A similar study was performed on embryo recipient cattle. In this study 50 heifers were injected with 5mg ibuprofen lysinate 1 hour prior to embryo transfer (Elli et al. 2001). The results showed that the treatment

animals had significantly higher pregnancy rates (86%) than the control heifers (56%).

In addition, it has been discovered that beef cattle that have grazed on endophyte-infected tall fescue have elevated $PGF_{2\alpha}$ in the plasma (Seals et al., 1998)

High levels of plasma $PGF_{2\alpha}$ have been shown to decrease pregnancy rates in cows. In addition, $PGF_{2\alpha}$ is an embryo toxin that affects embryos in the morula stage of development (Donaldson, 1986). Wiltbank et al. (1989) discovered that prostaglandin $F_{2\alpha}$ enhances the influx of intracellular Ca. This increase in Ca may interfere with the compaction process and prevent blastoceole formation (Schrick et al., 1999).

SUMMARY

An embryo transfer program must have all entities involved operating as efficiently as possible if an ET program is to be successful. Donors must be producing consistent, quality eggs, technicians must be highly skilled, and recipients must be suited for the task. The factors effecting recipients discussed above are certainly not an all-inclusive list. There are definitely other things that may influence a recipients' ability to carry an embryo to term. However, those factors discussed above have been studied and progress has been made concerning them.

A good nutrition program that leads to a physically healthy, moderately conditioned heifer has proven successful in ET programs. Managing mature, reproductively sound heifers in a stress free environment has also been shown to improve

results in an ET program. Combining and properly managing what has been learned concerning nutrition, BCS, site of embryo deposition, heifer age, and heat stress will surely aid in the success of an embryo transfer program.

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