PROGESTERONE AND FERTILITY

George E. Mann[1]

ABSTRACT

Fertility in the modern dairy cow is currently low and appears to be declining. Poor fertility is due to a number of factors, one of which is inadequate progesterone secretion by the mother during early pregnancy. While the reasons for poor progesterone secretion are still to be fully elucidated a number of factors have been implicated. Treatment with progesterone can yield improvements in pregnancy rate but it is important to ensure that treatment is administered at an appropriate time and targeted at those cows that actually need it.

INTRODUCTION

In the wild ancestors of the modern dairy cow fertility is high, with first service pregnancy rates approaching 90% leading to most cows calving within an 8 week period. Despite continued efforts to improve fertility, these figures represent little more than a dream to the modern dairy farmer. Poor fertility is a major problem and in many countries is approaching a level where sustainability of the industry is seriously threatened. Increased infertility means increased involuntary culling and hence an increased requirement for replacement heifers. In many situations, fertility has fallen to a level where the demand for these replacement heifers cannot be met within a herd. Furthermore, the problem is getting worse. While the aim of this review is to discuss the importance of progesterone concentrations during early pregnancy it is critically important to remember that fertility in the modern dairy cow is a complex multi-factorial problem. It depends on physiological capabilities, her health status, how she is fed and how she is managed.

THE DECLINE IN FERTILITY

Over the past 20 years, in the UK, calving rate to first service has fallen from around 60% to 40% (Royal et al., 2000), a decline of 1% per year. Similar declines have been seen in USA (Lucy, 2001). However, calving rate is only half the story: in order to conceive the cow must first present for mating. Current estimates put heat detection rates at little over 50%. This heat detection rate of 50% coupled with a calving rate of only 40% means that once a decision has been made to start mating, only 20% of potential mating opportunities result in a successful pregnancy. This decline in conception rate has been accompanied by an increase in the incidence of reproductive problems. For example, in the UK, the incidence of cows with reproductive cycle problems during the post partum period has risen from 32% to 44% over the past 20 years (Royal et al., 2000).

By combining a number of reports of conception rate collected from a number of countries a steady decline can clearly be seen (Figure 1). By fitting a line through these estimates, we can see that the situation is becoming critical, future predictions painting

[1]University of Nottingham, School of Biological Sciences
Division of Animal Physiology, Sutton Bonington Campus
Loughborough, LE12 5RD, UK

a grim picture. Over the last 50 years, the rate of decline appears to be in the order of 0.6% per annum. This decline has been linked to a number of changes within the dairy industry including increased milk yield, increased herd size, change in breed structure and changes in management strategy.

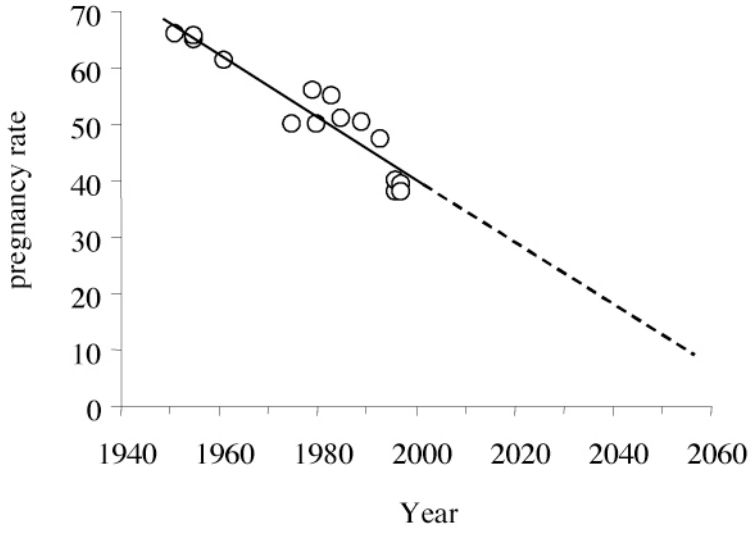

Figure 1. The decline in pregnancy rate over the past 50 years and predictions for the future. The fitted line shows a decline in pregnancy rate of 0.6% per annum. Each point represents an estimate of pregnancy rate from a study of lactating dairy cows (based on Mann, 2002).

THE TIMING OF LOSSES DURING EARLY PREGNANCY

The timing and extent of pregnancy losses has been reviewed extensively (Peters, 1996). However, while it is clear that in a typical dairy herd only 40% of cows calve to a particular service, it is less clear at what stage the 60% losses occur. Actual fertilisation rate is thought to be quite high (around 85 - 95%) indicating that in many animals an embryo does begin to develop. It is thought that around 5% of embryos are lost due to gross chromosomal abnormalities preventing development. This suggests that in some 80% of cows a potentially viable embryo is developing during the first week of pregnancy. However, by the end of the third week of pregnancy around 50% of cows recycle and come on heat again indicating a rate of early embryo loss of around 30%. Late embryo loss and abortion accounts for the loss of a further 10% of pregnancies resulting in a final calving rate of 40%. Some of the early embryo loss will result from a direct failure of embryo to development but the majority of this loss appears to result from a failure of the embryo to prevent luteolysis. This is supported by our recent studies in which we have flushed the uteri of mated cows on day 16, immediately prior to the potential onset of luteolysis. In these studies, we have found that around 85% of cows can have a developing embryo in the uterus at this time (Mann, 2001).

The establishment of pregnancy

In the cow the establishment of pregnancy depends on the effective functioning of an endocrine communication system between the mother and the embryo. This system underpins the decision, by the cow, to either maintain the corpus luteum and thus the pregnancy or to undergo luteolysis and reovulate, generating a new opportunity to become pregnant. In cyclic cows, luteolysis results from the release of luteolytic

episodes of uterine $PGF_{2\alpha}$, from the uterine endometrium, triggered by the development of oxytocin receptors. During early pregnancy in the cow, the embryo must inhibit this oxytocin stimulated $PGF_{2\alpha}$ release. The embryo achieves this by producing a protein, interferon tau, which acts locally within the uterus to inhibit $PGF_{2\alpha}$ secretion. This interferon tau protein is first detected in significant quantities in uterine flushes between days 14 - 16, when embryos have begun elongation (Robinson et al., 2006). To prevent luteolysis the embryo must be sufficiently well developed to allow the secretion of sufficient interferon - τ to prevent luteolytic $PGF_{2\alpha}$ secretion. Poor embryo development is associated with low interferon-τ production, failed inhibition of luteolysis and embryo loss (Mann & Lamming, 2001). A full understanding of the control of embryo development and interferon-τ production is therefore, of paramount importance in determining strategies to reduce the high level of early embryo mortality experienced in diary cattle. The principle hormone controlling this process is progesterone.

PROGESTERONE AND THE OUTCOME OF INSEMINATION

A number of studies have revealed a close association between progesterone concentrations in the mother and the adequacy of early embryo development (for reviews see Mann and Lamming 1999; Mann et al., 1999). Further use of milk progesterone analysis has revealed that during the postovulatory progesterone rise in mated cows there is a close relationship between progesterone levels on fertility. In a survey monitoring milk progesterone concentrations on day 5 in over 1400 cows, low progesterone concentration was associated with low pregnancy rates (Starbuck et al., 2001). Cows with adequate milk progesterone (>3 ng/ml) had pregnancy rates of around 50 - 55% while cows with poor milk progesterone had pregnancy rates as low as <10% in cows with milk progesterone levels of <1ng/ml (Figure 2).

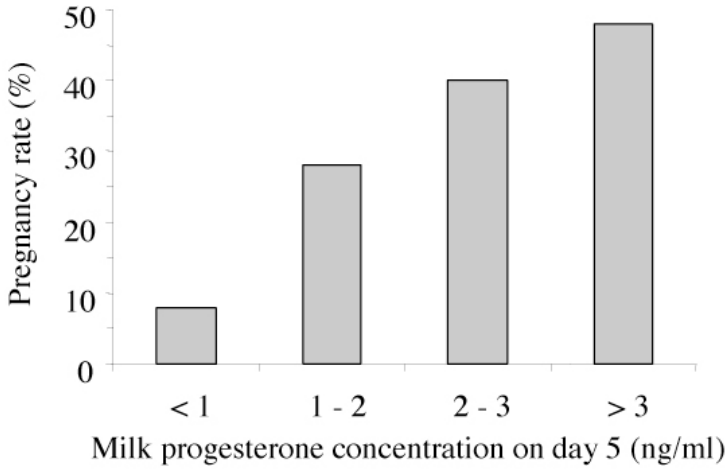

Figure 2. The effect of milk progesterone concentration on day 5 on pregnancy rate in dairy cows (based on Starbuck et al., 2001).

Further studies in inseminated cows have revealed close associations between plasma progesterone concentrations in the mother and development and interferon tau production by the embryo. For example, in a study in which cows were inseminated and blood sampled and then slaughtered on day 16 to collect embryos and assess interferon tau production, the presence of well developed embryos producing high levels

of interferon tau was preceded by elevated progesterone concentrations compared to cows with poorly developed embryos (Figure 3).

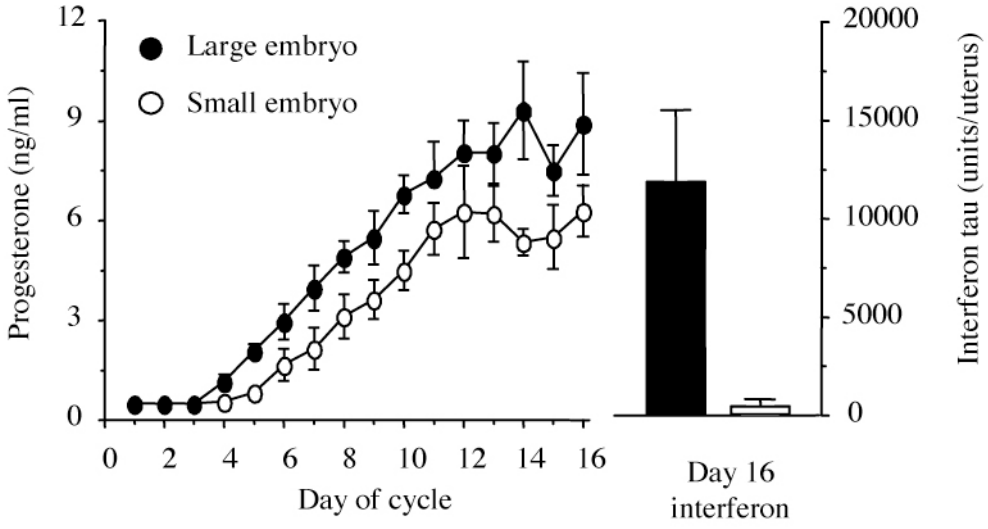

Figure 3. Plasma progesterone concentrations and uterine concentrations of interferon tau on day 16 in inseminated cows with large well developed or small poorly developed embryos (based on Mann et al., 1999).

In cattle, treatment with progesterone from day 2 - 5 has been shown to result in a 10 fold increase in conceptus elongation on day 14 (Garrett *et al.* 1988). Later increases in progesterone have failed to cause any marked increase in embryo development (Kerbler et al. 1997). In a further study we found that administration of progesterone from day 5 - 9, but not from day 12 - 16 resulted in a significant increase in interferon tau production on day 16 (Mann et al. 2006). Thus it would appear that it is the time at which progesterone secretion is initiated that is the critical factor in the control of early embryo development rather than the level to which progesterone rises.

FACTORS AFFECTING PROGESTERONE

While the detrimental effects of poor progesterone secretion, particularly during the postovulatory progesterone rise, have been established the causes of poor progesterone secretion are less clear. There is some evidence to suggest that plasma progesterone concentrations can be influenced by nutrition. Studies in beef heifers have demonstrated an increase in plasma progesterone in animals fed calcium soaps of long chain fatty acids to raise serum lipids (Hawkins et al., 1995), perhaps due to a reduced rate of progesterone clearance from the circulation. Moderate increases in progesterone concentrations have also been reported in dairy cows (Carroll et al., 1990), though with no associated increases in fertility. Feeding of supplemented fats from other sources has also been shown to increase circulating concentrations of progesterone (Talavera et al., 1985).

Rather than find a definitive cause of poor progesterone secretion, the current conclusions from a range of studies at Nottingham is that this phenomenon is a multi factorial issue with no simple causes. However, our studies have revealed a modest association between low concentrations of progesterone on day 5 of pregnancy and reduced body condition score and plasma leptin concentrations and an increased

incidence of sub clinical ketosis. This suggests poor energy status as, at least, a partial cause of poor postovulatory progesterone secretion.
Recent studies have reported reduced progesterone concentrations in high yielding dairy cows while others have found no relationship (Strong et al., 2005). In our studies at Nottingham we have found no relationship between milk yield and milk progesterone concentrations 5 days after mating (Figure 4).

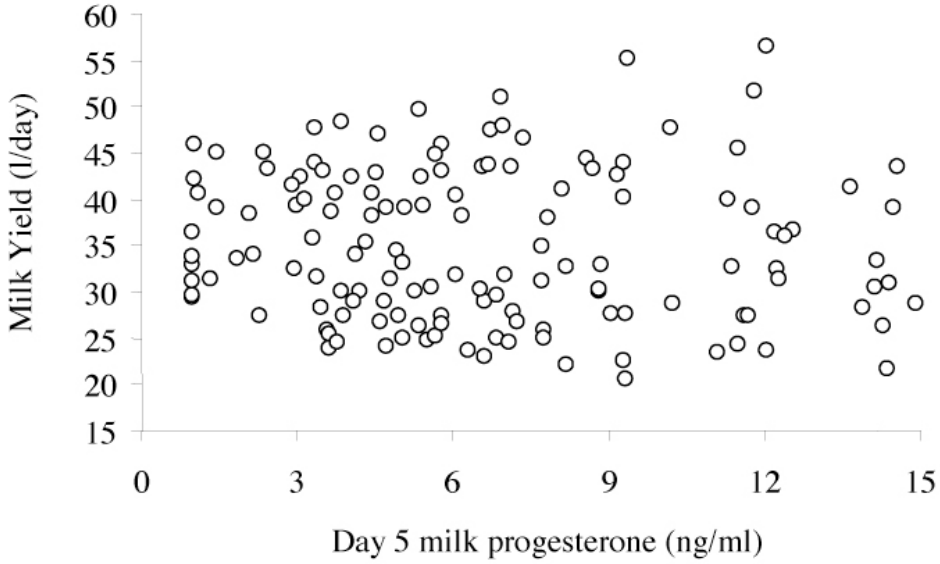

Figure 4. Relationship between milk yield and milk progesterone concentration 5 days after 1st insemination in Holstein Friesian dairy cows.

A number of diseased have a major effect on reproduction in the cows. One disease of particular importance is bovine viral diarrhoea virus (BVDV). This disease is a major cattle pathogen responsible for a spectrum of symptoms, including reproductive failure. For example, infection during oestrus can reduce conception rates by as much as 50% (McGowan et al., 1993) and BVDV can infect all the major cell types within the reproductive tract. However, the mechanism/s underlying its adverse effect on fertility has not yet been elucidated. One possible mechanism of action is through the disruption of ovarian function as studies have demonstrated that infection with BVDV can lead to a reduction in progesterone concentrations, the hormone essential for successful embryo development and establishment of pregnancy.
In a recent study in dairy cows we have shown no effect of BVD status per se on conception rate. However, an analysis of 70 dairy cows from the University herd has revealed lower day 5 milk progesterone concentrations and reduced conception rate to 1st AI (12.5% compared with 48.4%) in cows that underwent seroconvertion during the insemination period. Thus seroconversion may be the key factor in establishing the effects of BVDV on fertility. This finding may also apply to other diseases.

THE NEED TO TARGET PROGESTERONE TREATMENT

As early as the 1950s studies were being carried out to investigate progesterone supplementation as a means to improving conception rates. Since then, numerous studies have examined the effects progesterone supplementation on pregnancy rate in cattle (for review see Mann & Lamming, 1999). In these studies, a range of different cows have been treated with different progesterone therapies over a range of different

time periods. While many of these studies have demonstrated improvements in pregnancy rate, others have not. Furthermore, in many studies animal numbers are not sufficient to allow meaningful statistical analysis to be undertaken. In an overall analysis of 17 such studies (Mann & Lamming, 1999), we found a modest, though highly significant, 5% enhancement of overall pregnancy rate following progesterone supplementation. However, further analysis revealed that the timing of progesterone supplementation and the initial fertility of the animals being treated are both critical factors in determining the outcome of treatment (Figure 6). Earlier supplementation results in increased pregnancy rates compared to later treatment while treatment of cows with a problem yields better results than treatment of cows with good initial fertility. If studies are arbitrarily split into those in which initial fertility was “good” (conception rate over 50%) and those in which it was “poor” (conception rate under 50%), treatment was only of benefit in cows with “poor” fertility where increases in conception rate of almost 20% were observed.

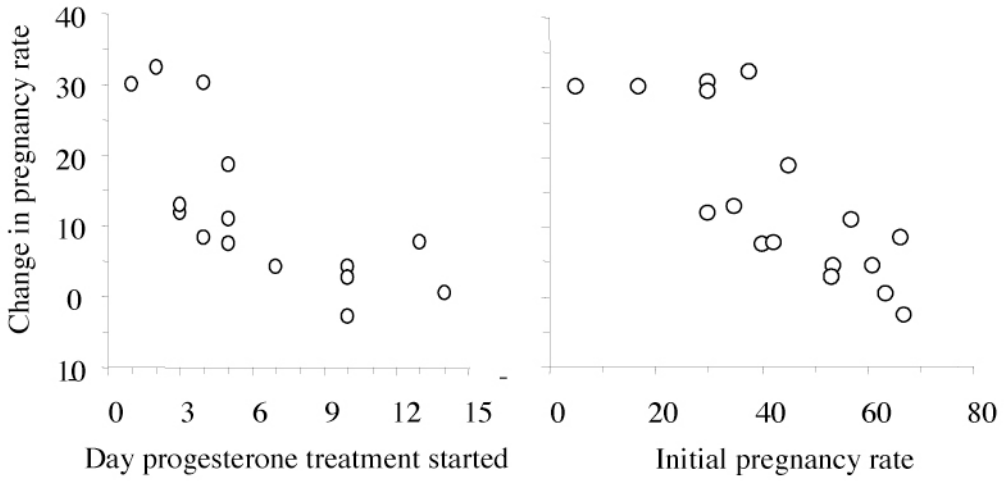

Figure 5. Both the first day of progesterone treatment and the initial fertility of the treated cows can affect the improvement in pregnancy rate achieved in progesterone supplementation studies. (Based on data reviewed in Mann and Lamming, 1999).

In a study using milk progesterone analysis was on day 5 following mating to target progesterone supplementation to specific cows with a specific progesterone deficiency (Starbuck et al., 2001), pregnancy rate was increased from 29% to 58% in cows with specifically targeted progesterone deficiencies. Thus by targeting progesterone treatment at an appropriate time to cows with a particular problem large benefits can be achieved. While blanket treatment does incur some benefit, the relatively small improvement in fertility does not warrant the effort and expense involved.

CONCLUSIONS

Dairy cow fertility is currently low and appears to be declining. A large body of evidence suggests that adequate progesterone production is critical to successful early embryo development and the production of adequate quantities of interferon tau to successfully establish pregnancy. Without sufficient progesterone secretion the pregnancy is likely to

fail and the cow recycle. Supplementation with progesterone can reverse this problem, but only if progesterone is administered at the correct time.

FUTURE PERSPECTIVE

Dairy cow fertility is a complex problem, controlled by a variety of factors including the cows inherent physiological capabilities, how she is fed and how she is managed and what health problems she is exposed to. There are no definitive causes of poor fertility: for every cause identified there are cows exhibiting extreme forms of the particular problem and good fertility. In addressing fertility problems a number of approaches have provided some small-scale gains, but many have failed to deliver any improvement in fertility at a national level. To achieve gains at this level requires a co-ordinated, multidisciplinary approach to the problem.

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