
THE PROCEEDINGS OF THE
NEW ZEALAND SOCIETY
OF
ANIMAL PRODUCTION

VOLUME 62 2002

New Zealand Society of Animal Production online archive

This paper is from the New Zealand Society for Animal Production online archive. NZSAP holds a regular annual conference in June or July each year for the presentation of technical and applied topics in animal production. NZSAP plays an important role as a forum fostering research in all areas of animal production including production systems, nutrition, meat science, animal welfare, wool science, animal breeding and genetics.

An invitation is extended to all those involved in the field of animal production to apply for membership of the New Zealand Society of Animal Production at our website www.nzsap.org.nz

View All Proceedings Next Conference Join NZSAP

The New Zealand Society of Animal Production in publishing the conference proceedings is engaged in disseminating information, not rendering professional advice or services. The views expressed herein do not necessarily represent the views of the New Zealand Society of Animal Production and the New Zealand Society of Animal Production expressly disclaims any form of liability with respect to anything done or omitted to be done in reliance upon the contents of these proceedings.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

You are free to:

Share— copy and redistribute the material in any medium or format

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made. You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

NonCommercial — You may not use the material for commercial purposes.

NoDerivatives — If you remix, transform, or build upon the material, you may not distribute the modified material.

http://creativecommons.org.nz/licences/licences-explained/

Mathematical modelling of anoestrus in dairy cows and the linkage to nutrition

J. F. SMITH, T.K, SOBOLEVA, A.J. PETERSON, A.B. PLEASANTS,
L.M. CHAGAS[1] and C. R. BURKE[1]

AgResearch Limited, Ruakura Research Centre, Private Bag 3123, Hamilton,New Zealand

ABSTRACT

Postpartum anoestrus is a major reproductive problem in New Zealand dairy cows and its duration is related to the nutrition levels both pre and post calving. However, the mechanistic details of this relationship are largely unknown. A better understanding of the interactions between nutritional status, and the levels of the reproductive hormones controlling follicle development and ovulation is needed. A mathematical model consisting of a set of interactive non-linear differential equations and describing the dynamics of the interactions among luteinising hormone (LH), follicle stimulating hormone (FSH) and oestradiol was developed. The model depicts oestradiol profiles generated by individual follicles from the first follicular wave after calving until ovulation, and changes in LH pulsatility leading to the first pre-ovulatory surge are also produced. The robustness of the model was ascertained from iterative processes, and it was also checked against existing experimental data so as to mimic observed changes in hormone levels. It was shown that two mathematical parameters which control: i) the speed of changes in the feedback of LH activity to oestradiol; and, ii) the sensitivity of the ovarian response to LH, have the greatest effect on duration of anoestrus.

Keywords: mathematical model; anoestrus; dairy cows; nutrition; oestradiol; LH; FSH.

INTRODUCTION

Postpartum anoestrus is a major reproductive problem in New Zealand dairy cows. Animals with an extended postpartum anoestrous interval (PPAI) are not cycling at the time of planned start of mating and are a major contribution to low submission rates. This is a major problem in trying to maintain the annual concentrated calving pattern required in dairy cows under the seasonal production, pasture based systems used in New Zealand (Macmillan & Clayton, 1980).

While the duration of anoestrus is related to the nutrition levels both pre- and post calving (Chagas *et al.*, 2001; Lucy, 2003), the mechanistic details of this relationship are largely unknown. To resolve the anoestrous problem, a better understanding of the interactions between nutritional status and the levels of the reproductive hormones controlling follicle development and ovulation is needed.

Our approach to this has been to construct a theoretical (mathematical) model because by constructing a dynamic model such that the equations are associated with the elements of the biology, then hypotheses about different aspects of the whole process can be tested more precisely. The use of this type of model will enable us to become more informed about the interactions involved and will allow field experiments to be better designed and target more specifically those process highlighted by the model.

McDougall *et al.* (1995) have shown that postpartum anoestrus is not due to the lack of follicle recruitment, but to the failure of the large (dominant) follicle to attain the level of oestradiol production necessary for ovulation.

The PPAI is dependent on the number of follicular waves that take place between parturition and ovulation and this can vary from one to nine (McDougall *et al.*, 1995).

The wave-like pattern of ovarian follicular activity during the bovine oestrous cycle was first predicted by Cupps *et al.* (1959) and confirmed by Rajakoski (1960). Since then intensive investigation of follicular dynamics in both sheep and cattle has resulted in many reviews (Lucy *et al.*, 1992). In this paper, we have used the terminology describing folliculogenesis proposed by Scaramuzzi *et al.* (1993) and the conceptual model of Ginther *et al.* (1996).

This paper presents a mathematical model developed to describe the dynamics of the interactions among luteinising hormone (LH), follicle stimulating hormone (FSH) and oestradiol (E_2) from parturition to ovulation. A model (Soboleva *et al.*, 2000) that describes bovine follicular development and ovulation rate was adapted to include the pre-ovulatory follicular waves encountered in anoestrus as well as the changes in the hypothalamic-pituitary feedback that occurs during this time.

The modified model depicts oestradiol profiles generated by individual follicles from the first follicular wave after calving until ovulation and changes in LH pulsatility leading to the first pre-ovulatory surge are also produced. The frequency of LH pulses increases during the duration of each wave and also systematically during the postpartum period because the dominant follicle gets bigger on average each subsequent wave and because of changes in sensitivity of the pituitary gland to oestradiol produced by the growing follicles.

---

[1] Dexcel Limited, Private Bag 3221, Hamilton,New Zealand

MATERIALS AND METHODS

Development of the model

The modified model consists of a set of interactive non-linear differential equations that describe the dynamics of follicle development and the interactions among LH, FSH and oestradiol. To formulate the system of differential equations describing the fate of every follicle the following criteria were adopted:

1. the oestradiol secretion rate of an individual follicle is a measure of its maturity;
2. the maturation rate of each follicle at any time depends on its current maturity and on circulating concentrations of oestradiol and other hormones, e.g. FSH, LH;
3. the factors controlling follicular growth are the same for all follicles;
4. the circulating concentration of oestradiol at any time is the sum of the contributions made by each follicle;
5. the more oestradiol a dominant follicle produces, the greater is the potential to produce oestradiol until oestradiol production is such that an LH surge is induced leading to ovulation;
6. within a group of growing follicles, the larger dominant follicles act to inhibit and eventually to decrease the growth of subordinate follicles;
7. at commitment, no two follicles are at identical stages of development;
8. once a follicle is committed to grow, then growth of that follicle is uninterrupted until either it becomes atretic, or in the case of the final follicular wave, it ovulates;
9. the pattern of LH pulse frequency post partum is a reflection of the changing sensitivity of the hypothalamic-pituitary complex to oestradiol over time;
10. the rate of follicle growth and oestradiol production is dependent on the level of follicular sensitivity to pituitary LH production;
11. for the purposes of the model, we consider the hypothalamus as a simple pacemaker with a frequency controlled by a hormonal signal generated by the ovary; and
12. the role of FSH in this simplified consideration is restricted to the stimulation of new follicle commitment and the level of FSH is regulated through the feedback of oestradiol from growing follicles.

Based on these assumptions, the model was constructed. In its conceptual form it is presented in Figure 1.

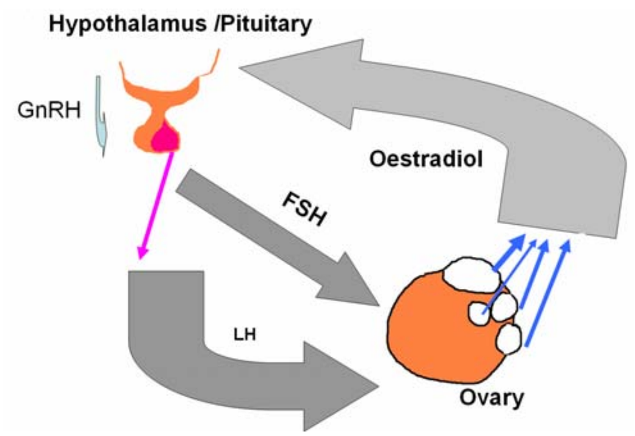
Mathematically, it is comprised of the following equations:

FSH stimulation of follicle commitment
Equation 1:

$$\frac{df}{dt} = \beta \cdot f \cdot \left[\beta_1 - \frac{d}{dt}\max(x_i) \right]$$

Every time, when the level of FSH (f) in the system reaches (exceeds) some level $f = f_0$, new commitment starts. The level of FSH is regulated through oestradiol feedback from growing follicles and *max*(x_i) is the oestradiol production by the dominant follicle. β is a parameter that characterises the rates of FSH increase/decrease.

FIGURE 1: Schematic outline of the conceptual hormonal interactions in the model



Oestradiol production (Equation 2): Let x_i be the oestradiol produced by the i^{th} follicle (i=1, 2,…, N) where N is total number of committed follicles at time t. The number of growing follicles and initial values of oestradiol x_i are taken at random and independently for each new wave. A mature follicle is considered to reach ovulation when x_i =1. Equation 2 is actually a set of N equations.

$$\frac{dx_i}{dt} = k \cdot x_i \cdot (1 - x_i) \cdot \left[y + \kappa \cdot LH - (\mu - x_i)\sum_i^N x_i \right]$$

Sensitivity of follicle to LH; part of Equation 2: $y + \kappa \cdot LH$ plays a role of a 'support function' for follicles development. One of the committed follicles ovulates when this function approaches 'μ^2'. For convenience this function has been divided into two parts: LH-dependent and an LH independent part 'y'. The sensitivity of the ovaries to LH is characterised by 'κ' and the positive variable 'μ' can be identified with the rate of E_2 production by each follicle.

Changes in function **'*y*'** reflect changes in the sensitivity of the hypothalamus to E_2 produced by the growing follicles.

Equation 3

$$\frac{dy}{dt} = -\frac{a \cdot [\max(x_i) - mean(x_i)]}{1 + b \cdot t}$$

'y' is re-set at each wave of follicular commitment to a level, that would enable ovulation to occur, as follicles grow and produce more oestrogen 'y' decreases and the follicle becomes atretic. For each successive follicular wave, the rate of this decrease diminishes until the decrease in 'y' becomes low enough to allow ovulation to occur. Parameter 'b' determines the pattern of this change in the decrease in 'y'. This change over time can be viewed as either: 1) a decrease in 'negative' E_2 feedback; or, 2) an increase in 'positive' E_2 feedback.

LH production (Equation 4). The equation for LH describes the release of LH by the pituitary and is interconnected with other equations (5 & 6) that describe hypothalamus activity. Parameters ***'p', 'v'** and **'A'*** define the 'pacemaker' for LH pulsatility (amplitude and frequency) while ***'c'*** is the degradation (or clearance) rate of LH.

$$\frac{dLH}{dt} = l \cdot v_p^+ - c \cdot LH \quad , \quad v_p^+ = \begin{cases} v_p \, , & v_p \geq 0 \\ 0 \, , & v_p < 0 \end{cases}$$

Pulse generator- (Equations 5 & 6*)*. This represents the GnRH pulse generator that controls the pituitary release of LH. A pulse occurs when 'v_p' is positive.

$$\frac{dv_p}{dt} = A\left(1 - \frac{\alpha}{1 + b \cdot t}\right)\left(\frac{1}{1.01 - \max(x_i)}\right) \cdot \sin p$$

$$\frac{dp}{dt} = v_p$$

LH pulse frequency and oestradiol feedback: The changes of the frequency of LH pulses are characterised by factors in Equation 5.

$$\left(1 - \frac{\alpha}{1 + b \cdot t}\right) \cdot \left(\frac{1}{1.01 - \max(x_i)}\right)$$

The frequency increases during the duration of each follicular wave and systematically during the postpartum period because the dominant follicle of each wave is getting bigger and because of changes in feedback to oestradiol '*b*' (the same factor as in Equation 3.

All the above equations are solved simultaneously.

Values for the various parameters were derived from typical values in the published literature. An example of the values used is: ($\beta = 30$; $\beta_1 = 1/300$; $k = 12.5$; $\kappa = 0.005$; $\mu = 0.55$; $a = 0.56$; $b = 0.012$ (range 0.001 to 0.3); $l = 0.575$; $c = 7$; $\alpha = 0.1$; $A = 2000$).

For the calculations we use our equations in dimensionless form, thus there are no units on the parameters.

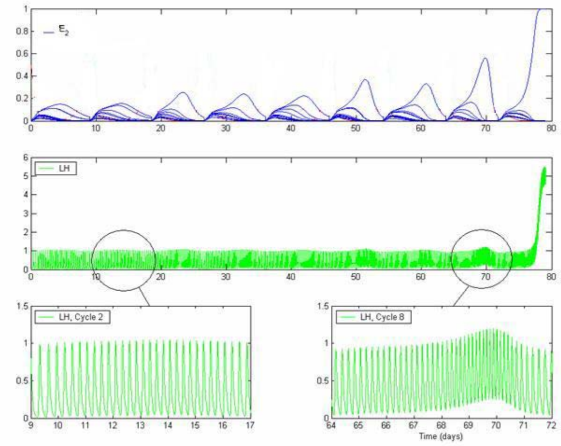
It should be noted that the model deals simultaneously with processes that operate on different time scales (e.g. from minutes for the hypothalamic pulsatility to days for follicle growth and weeks for changes in feedback function). Because of these different time scales, the range of the unknown parameters in the model is restricted by the requirement to maintain the robustness and stability of the model. This was ascertained from iterative processes and the model was also checked against additional experimental data so as ensure that it mimics observed changes in hormonal levels.

RESULTS AND DISCUSSION

The model depicts oestradiol profiles generated by individual follicles from the first follicular wave after calving until ovulation. Changes in LH pulsatility leading to the first pre-ovulatory surge are also produced. The frequency of LH pulses increases during the duration of each wave and also systematically during the postpartum period because the dominant follicle becomes larger on average each subsequent wave and because of changes in sensitivity of the pituitary gland to oestradiol produced by the growing follicles. This is shown in Figure 2.

FIGURE 2. An example of numerical simulation based on the Equations 1 to 6.
Note that LH pulse frequency and amplitude is influenced by oestradiol levels.

In the upper box the scale for the E_2 has been normalised to the peak at ovulation and each line represents the E_2 production of each committed follicle. In the lower box each peak represents the instantaneous level of LH. The frequency of LH pulses increases during the duration of each wave and also systematically during the postpartum period.



Although the pattern of ovarian follicle development during anoestrus is governed by each of the described factors, the duration of the PPAI is most sensitive to; 1) speed of changes in the feedback of hypothalamus activity to oestradiol (parameter ***'b'*** in the model); and, 2) the response of the ovary to LH, characterised by parameter '**κ**' in the model.

The ruminant placenta produces copious amounts of steroids (e.g. oestradiol) during late pregnancy (Peterson *et al.*, 1975) and this has a suppressive effect on the reproductive hormones of the hypothalamus and pituitary gland. The first phase of postpartum reproduction is the recovery of the hypothalamus and pituitary gland from these suppressive effects and the resumption of FSH secretion and pulsatile LH release (Lucy, 2003). This recovery in sensitivity is depicted in the model by parameter ***'b'.*** Simulations from the model show that the PPAI reduces as '***b***' increases (Figure 3).

If we interpret an increase in '***b'*** as the recovery of hypothalamic sensitivity to oestradiol, then it is apparent from the figure that once a value of 0.065 for '***b'*** is reached then full sensitivity has been attained and no further reduction in PPAI is possible. However, at lower levels of '***b'*** the PPAI is very sensitive to changes in value. Figure 4 illustrates this by showing the marked changes in PPAI produced by such changes in parameter '***b'*** and the resulting smaller number of follicular waves between parturition and ovulation.

FIGURE 3. Results of simulations from the model showing the relationship between changes in parameter '***b'*** and PPAI. If parameter '***b'*** equates to the recovery of hypothalamic sensitivity to oestradiol then it is apparent from the figure that once a value of 0.065 for '***b'*** is reached then full sensitivity has been attained and no further reduction in PPAI is possible. However, at lower levels of '***b'*** the PPAI is very sensitive to changes in value of '***b'***.

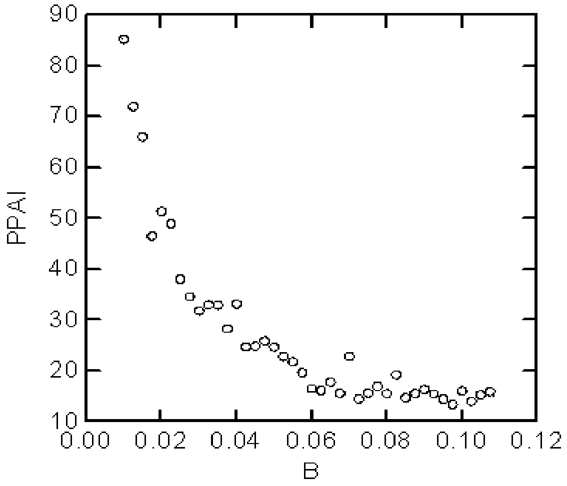
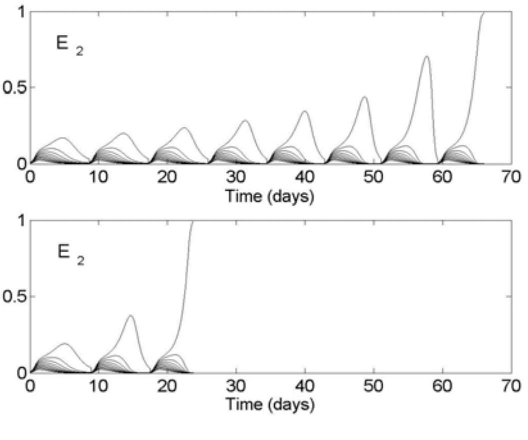


FIGURE 4. Illustration of the change in oestradiol production for successive follicular waves. When the model parameter '*b'* is increased from 0.015 to 0.05 (4 fold) there is a resulting (2.73 fold) reduction of PPAI from 68 to 25 days.
(As in Figure 3 each line represents the E_2 production of each follicle. The lower panel shows the reduced number of follicle waves prior to ovulation when the hypothalamic sensitivity to E_2 is increased.)



This indicated that further development had to be aimed at providing a biological explanation for the two most important mathematical parameters through linking the changes in PPAI to changes in certain metabolic hormones so as to provide an understanding of the interaction of nutrition and anoestrus.

The first of these developments (Pleasants *et al*., 2005) shows that the model has linked variations in the postpartum anoestrus interval to changes in certain metabolic hormones, providing an explanation for the mechanism by which nutrition influences anoestrus. Parameter '***b'*** and factor 'κ' appear to reflect the level of prepartum plasma growth hormone concentrations and postpartum levels of insulin, respectively.

Further steps in our research are being undertaken to provide for the inclusion of genetic components to accommodate different genotypes**.**

The value of such models for resolving genotypic effects has already been demonstrated by the use of the original 'ovulation model' to determine the mechanism of genetic differences in ovulation rate of pigs (Soboleva *et al.,* 2004).

ACKNOWLEDGEMENTS

This joint AgResearch and Dexcel project was funded by New Zealand Dairy Farmers through Dairy InSight.

REFERENCES

Chagas L.M.; Clark B.A.; Gore, P.J.S.; Morgan, S.R. ; Verkerk, G.A. 2001: Postpartum anoestrous interval and metabolic changes in heifers supplemented with pasture pre-calving. *Proceedings of New Zealand Society of Animal Production 61:* 188-191

Cupps, P.T.; Laben, R.C.; Mead, S.W. 1959: Histology of pituitary, adrenal, and reproductive organs in normal cattle and cattle with lowered reproductive efficiency. *Hilgardia 29:* 383–410

Ginther, O.J.; Wiltbank, M.C.; Frike, P.M.; Gibbons, J.R.; Kot, K. 1996: Selection of the dominant follicular in cattle. *Biology of reproduction. 55:* 1187–1194

Lucy, M.C. 2003: Mechanisms linking nutrition and reproduction in postpartum cows. *Reproduction, Supplement 61:* 415-427

Lucy, M.C.; Savio, J.D.; Badinga, L.; De La Sota, R.L.; Thatcher, W.W. 1992: Factors that affect follicular ovarian dynamics in cattle. *Journal of animal science 70:* 3615–3626

Macmillan, K.L.; Clayton, D.G. 1980:.Factors influencing the interval to postpartum oestrus, conception rate and empty rate in an intensively managed dairy herd. *Proceedings of the New Zealand Society of Animal Production 40:* 236-239

McDougal, S.; Burke, C.R.; Macmillan, K.L.; Williamson, N.B. 1995: Patterns of follicular development during periods of anovulation in pasture-fed dairy cows after calving. *Research in veterinary science 58:* 212-216

Peterson, A.J.; Hunter, J.T.; Fairclough, R.J.; Welch, R.A.S. 1975: Oestrogens in bovine foetal and maternal plasma near term. *Journal of reproduction and fert*ility *43:* 179-181

Pleasants, A.B; Chagas, L.M; Burke, C R.; Smith, J. F.; Soboleva, T.K.; Peterson, A.J. 2005: Relationships among metabolic hormones, luteinising hormone and anoestrus in dairy heifers fed two nutritional levels. *Proceedings of the New Zealand Society of Animal Production 65:* 329-334

Rajakoski, E, 1960: The ovarian follicular system in sexually mature heifers with special reference to seasonal, cyclical, and left–right variations. *Acta endocrinologica 34:* Supplement 52, 7–68

Scaramuzzi, R.J.; Adams, N.R.; Baird, D.T.; Campbell, B.K.; Downing, J.A.; Findlay, J.K.; Henderson, K.M.; Martin, G.B.; McNatty, K.P.; McNeilly, A.M.; Tsonis, C.G. 1993: A model of follicular selection and the determination of ovulation rate in the ewe. *Reproduction, fertility and development 5:* 459-478.

Soboleva, T.K.; Peterson, A.J.; Pleasants, A.B.; McNatty, K.P.; Rhodes, F.M. 2000: A model of follicular development and ovulation in sheep and cattle. *Animal reproduction science 58:* 45-57

Soboleva, T.K.; Pleasants, A.B.; van Rens, B.T.T.M.; van der Lende, T.; Peterson, A.J. 2004: A dynamic model of ovulation rate reveals an effect of the oestrogen receptor genotype on ovarian follicular development in pigs. *Journal of animal science 82:* 2329–2332