Relationship between production and reproduction

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Abstract
Genetic selection for yield has occurred in association with a reduction in fertility. This contributes to high culling rates and a reduced life expectancy for Holstein cows. Higher yielding cows have been genetically selected to mobilise tissue at the start of lactation, thus enhancing milk production but placing the cow into a prolonged state of negative energy balance. The endocrine and metabolic signals associated with NEB signal to the reproductive tract, resulting in less regular oestrous cycles and reduced embryo survival rates. The negative relationship between yield and fertility is complicated by a variety of other factors. Metabolic and infectious diseases depress both yield and fertility and may be more influential than production level in some herds. The links between yield, metabolic hormones and fertility also alter as the animal matures. Thus fertility in maiden heifers is generally good in high genetic merit animals which mature younger, but may be compromised to a greater extent in the first lactation when higher rates of tissue mobilisation can occur. Over conditioned animals at calving are particularly disadvantaged as they are more likely to experience calving difficulties and appetite depression. The metabolic status at the start of each lactation will be influenced by events occurring earlier in the animals' life and thus individual lactations cannot be considered in isolation..

Introduction
The past 40 years have seen a number of significant changes in the dairy herd. These include: (1) a major rise in milk yield per cow; (2) an increased use of the Holstein breed; (3) an increase in average herd size and (4) a reduction in fertility (Royal et al. 2000; Lucy, 2001). There is widespread international concern at the decline in both fertility and longevity in dairy cows. The average herd life of UK Holsteins is currently 3.4 lactations, whereas economic calculations in the US indicate that a cow needs to achieve a herd life greater than 5 years for optimum productivity (Jagannatha et al. 1999). Annual culling rates in the UK and Canada are around 30%, of which around one third are due to infertility, which remains the main reason for culling (Esslemont and Kossaibiti, 1997; Durr et al. 1997; Whitaker et al. 2000). These figures fail, however, to account for the many losses which occur before a cow even reaches the start of her first lactation (Table 1). A number of countries are now including fertility as well as productivity traits in sire selection programmes, in an effort to improve the situation. The first aim of this paper is to provide a physiological basis which shows why production and reproduction are inextricably linked. The second is to show that these relationships alter at different times in the life history of the individual animal.

Changes in metabolic status associated with the onset of milk production
When a cow calves she undergoes a number of metabolic adaptations for lactation which are driven by the endocrine system. These are modified by her nutritional status both in terms of actual food consumed at the time and body condition, which represents a reserve of additional nutrients which can be utilised. As cows have been selected for increasing yield, animals have been produced which have altered their priorities for nutrient partitioning so that more body

tissues are mobilised to support milk yield in early lactation and more feed is targeted into milk rather than being used to replenish body condition as the lactation progresses.

Table 1. *Summary of losses occurring between insemination of a multiparous dam and the start of the first lactation of the offspring.*

Stage of life	Starting No.	% died/culled	Reasons
Insemination	100		
Fertilization	90	10%	Fertilization failure, wrong time AI
Pregnant at 24 days	54	40 %	Early embryo loss*
Pregnant at 2 mo	42	20%	Late embryo loss*
Parturition	40	5%	Abortion
Alive at 24 h	37	7%	Perinatal mortality+
Heifer alive at 24 h	19	50%	Male calves
Alive at 1 month	18	2%	Neonatal mortality
Alive at 15 month	17	7%	Juvenile mortality
Pregnant as heifer	16	8%	Conception failure
Calved	15	5%	Later fetal loss/abortion
Start first lactation	14#	3%	Maternal death at calving

Notes
* Embryo losses are lower in maiden heifers, total about 30%
+ Perinatal losses of calves are higher at first calvings, about 12%.
# Of the 14 calves born at this time, 12% will experience perinatal losses and half will be male. Therefore, following a single AI, only about 7 heifer calves are produced to rear and potentially contribute to the next generation.
Data from: Roy, 1990; Mann et al. 1999;Lucy, 2001; own unpublished observations.

The most important endocrine system involved is the somatotrophic axis and within this system the supply of glucose is a critical component. Glucose is transferred across the mammary gland as the precursor for milk lactose. As a result less glucose is available for uptake into other body tissues, a process which is driven by insulin. Circulating insulin concentrations are also in higher genetic merit cows (Taylor et al. 2003a). The requirement to maintain blood glucose concentrations in early lactation causes an up-regulation of gluconeogenic mechanisms in the liver.

The main lactogenic hormone in the cow is growth hormone (GH). When body reserves are adequate GH secretion by the pituitary stimulates production of insulin-like growth factor-I (IGF-I) by the liver. This growth factor circulates throughout the body where it has a wide variety of metabolic and proliferate effects on different tissues. Another site of GH action is in adipose tissue, where it acts to mobilise release of stored fatty acids into the blood. NEFAs provide an alternative energy supply to glucose via oxidation in the liver. They are also taken up by the mammary gland for incorporation into milk fat. Several factors are thought to act around calving to reduce the concentration of GH receptors in the liver while maintaining those present in adipose tissue. These include the decline in dry matter intake, the glucocorticoid surge and the fall in insulin secretion (Lucy et al. 2001). IGF-I production by the liver therefore falls quite steeply as IGF-I secretion becomes temporarily decoupled from GH. This in turn increases GH secretion through removal of negative feedback. GH receptors in adipose tissue are, however, not affected and the low insulin acting together with high GH secretion enhances tissue mobilisation leading to loss of body condition. As lactation proceeds several changes occur. As

feed intake increases and the cow's nutritional balance improves the GH-IGF-I link becomes re-coupled so circulating IGF-I concentrations rise. Insulin levels also tend to rise, a situation which alters the balance of nutrient partitioning, so more glucose is taken up into tissues other than the udder, becoming available as an energy source to the cow, rather than being lost to her in milk.
One other endocrine pathway which deserves brief mention is that related to leptin. This hormone is produced by adipose tissue and circulating concentrations are therefore positively related to the amount of fat present. Control of leptin secretion is however more complex, as circulating leptin concentrations falls at parturition in cows in advance of the subsequent loss in body condition (Kadokawa et al. 2000). One of leptin's main sites of action is in the hypothalamus where it is one of a variety of signalling molecules which are involved in appetite regulation. Dry matter intake in late gestation cows declines from about 14 days before calving, with a precipitous drop in the last 24 h score (Hayliri et al. 2002). Feed intake decreases over this period to a greater extent in cows with higher body condition scores (BCS) (Garnsworthy and Topps, 1982; Hayliri et al. 2002).
The immediate onset of lactogenesis is therefore associated with a period of depressed appetite and followed by a high rate of tissue mobilisation. Together these factors push the cow into a state of negative energy balance (NEB), when feed intake does not meet the energy requirements of the cow for maintenance, lactation and activity. In lower yielding cows this period of NEB may only last for a brief period of time (1-2 weeks) whereas high yielding cows may remain in a state of NEB for up to 15 weeks after calving (Taylor et al. 2004). Whilst this is good for milk production, it has a deleterious effect on fertility.

Link between energy balance and fertility.
There is no question that fertility is depressed when animals are in a state of NEB and genetic correlations between reproduction and milk yield are unfavourable (Pryce et al. 2004). This is likely to be based on a very primitive system that prevented animals reproducing when food was in short supply. In the dairy cow this manifests itself in a variety of ways. Milk progesterone profiles have proved a useful mechanism to monitor reproductive function. These have shown that higher yielding cows tend to remain acyclic for a longer interval after calving. Others experience irregular cyclicity with prolonged periods of either low progesterone (extended interluteal interval) or high progesterone (prolonged luteal activity). Thus in high yielding herds only around 40% of cows may be having regular oestrous cycles in the period leading up to first service (Opsomer et al. 1998; Taylor et al. 2004a). In itself this makes accurate oestrous detection much more difficult. Whilst difficult to prove, there is increasing evidence that modern high yielding dairy cows are also less likely to exhibit overt oestrous behaviour even if apparently having otherwise normal ovulatory periods. Furthermore, even if served at an appropriate time, cows do not necessarily conceive. The incidence of early embryonic mortality in UK herds is currently estimated to be around 40% (Mann et al.1999). The increase availability of ultrasonography for early pregnancy detection has shown that a further 20% of cows lose their embryos in the second month of pregnancy. All of these factors conspire to make fertility management more difficult for the herd manager, who also has to cope with an increased number of cows to look after, often without a concomitant increase in staff.
The positive link between increased yield and problems over fertility appears clear cut in most studies. In our work on UK herds we have found that animals reaching a peak yield of >42 kg/day are particularly vulnerable, showing a high proportion of abnormal oestrous cycles and a reduced conception rate (Wathes et al. 2001). Below this production output it is easier to maintain acceptable levels of fertility. Not all previous studies, however, agree to this link between yield and fertility and we suggest a number of reasons why this may be the case. Firstly, peak yield is more informative than 305 day yield, as the former reflects the situation more

accurately in early pregnancy when the cow is also being required to conceive. The definition of "high yielding" varies between counties in relation to the genetic merit of their herd, so some may have increased yield considerably without necessarily reaching the threshold above which the cow has more difficulty in coping. Another important consideration is that this link is much less marked in the first lactation, when cows have not yet reached their full production potential (see below). Finally, at the opposite end of the spectrum, the reverse situation applies. Thus we have found that within the herds we have investigated, the lowest yielding cows often also have fertility problems. A variety of conditions such as ketosis, lameness, mastitis and retained placenta may simultaneously depress both yield and fertility. In herds where management attention to detail is less than optimal disease may thus have a larger impact on overall herd fertility than high yield (Lucy, 2001).

A detailed analysis of the possible signalling mechanisms which link high yield to reduced fertility is outwith the scope of this paper and this topic has been reviewed previously (eg Beam and Butler, 1999; O'Callahan et al. 2001;Wathes et al. 2003; Taylor et al. 2004a). In brief, there is evidence that metabolic signals can act at the level of the hypothalamus to suppress LH secretion, the ovary to reduce follicular growth and oestradiol production and to reduce oocyte quality and the uterus to produce a less favourable environment for early embryo development. Many earlier investigations focussed on measuring a variety of blood metabolites (eg NEFAs, glucose, beta hydoxybutyrate, urea) and tried to link these to fertility status, often with limited success.

More recently there has been particular interest in the somatotropic axis outlined above involving IGF-I, insulin and GH. All of these hormones can be shown to influence reproductive function in work in cattle using *in vitro* approaches or by feeding experimental diets which make large alterations to nutritional status. Some, but not all, have also shown links in real herd situations. Our own work suggests that part of the reason for the confusion is that the relationships between metabolic status and fertility alter as cows age, and this has generally not been accounted for in earlier work. For example, the nadir in IGF-I concentration reached in the 1-2 weeks after calving is highly predictive of subsequent fertility in multiparous cows, whereas in primiparous animals this relationship does not hold true (Taylor et al. 2004b). Furthermore, there are major differences between countries in the genetic background of the animals used, the management systems including the way the cows are reared and fed and in the environment (extremes of heat and cold) which will also cause important differences. Our observations reported below refer to the UK situation over the past 10 years in studies of cows producing average yields in the range 8,000 – 14,000 kg per 305 day lactation.

Maiden heifers

Most UK dairy farmers aim to serve their heifers at approximately 15 months of age to calve at about 2 years. This does, however, vary considerably between farms with some serving heifers at only 13 months, whilst others delay by up to a year to calve at 3 years. Puberty in Holsteins occurs at about 9 months, but is dependent on animals having achieved an adequate body size. Growth rate peaks at about 13-14 months. Like milk yield, growth is regulated by the somatotrophic axis, with GH driven IGF-I being of particular importance for bone and muscle development (Le Roith et al. 2001). We have found that circulating IGF-I concentrations at 6 months are highly correlated with the growth rate. Therefore genetic selection for yield has also influenced growth rate and final size, with potentially higher yielding youngstock growing faster and maturing at a younger age (Sejrsen et al. 2000). Target growth rates are generally around 0.7 kg/day, although it has been suggested that these could be higher (0.9 kg/day) in higher genetic merit heifers (Dawson and Carson, 2004) and a variety of "stepped" regimes have been recommended with different rates at different ages (Margerison, 2004). There is considerable evidence that growing heifers too rapidly before puberty will reduce mammary growth and thus milk yield potential (Sejrsen et al. 2000). Despite such published recommendations we have recently found surprisingly wide variations in early growth rates (up to 6 months) between UK dairy farms with mean values ranging from 0.23-1.25 kg/day and there can also be large differences between individual animals within farms (unpublished observations). In addition to genetic potential, growth rate is clearly also affected by nutrient availability and by disease. Infection will cause a check to growth which may or may not be compensated for subsequently. The incidence of calf diseases will be strongly affected by such management factors as colostrum provision, housing and vaccination policy.

In terms of fertility, this is generally considered less of a problem in maiden heifers than in lactating cows. Pryce et al. (2002) reported first service conception rates of 64% and 71% in lines selected for high or average genetic merit. Current US guidelines are to inseminate dairy heifers at 60% of mature body weight. In our recent study of 111 heifers using exclusively AI, the conception rate to first service was 56%. Some heifers nevertheless required up to 5 services to conceive and 8% had failed to hold to service within the 4 month service period and were then left until the following season, when the majority then conceived to calve as 3 year olds (Swali, 2005). These animals which did not conceive in their first season were significantly lighter at the start of the service period and on average 14 days younger than the rest of the group. Age at first service, age at conception and age at calving were all highly positively correlated with size measurement made as juveniles, in particular weight at 6 months and weight change between 3-9 months. Furthermore, weight throughout the time period 3-15 months was also highly correlated with weight at first calving ($P<0.001$) (Swali 2005). In summary, early growth patterns are related to genetic merit, influenced by the rearing environment and affect the fertility such that animals which are better developed at 6 months of age conceive more readily and will thus calve at a younger age for the first time.

Primiparous cows

Animals calving for the first time are still not physically mature. It has been suggested that cows should calve at 82% - 90% matures body weight (NRC, 2001; Margerison, 2004). After calving they therefore need to use nutrients for continued growth as well as milk production. They have also not yet reached their full capacity for milk production, so yield in the first lactation is significantly lower than in subsequent years. These differences can be partly explained by measurements of circulating insulin and IGF-I, both of which are significantly higher in primiparous than multiparous cows (Wathes et al. 2001). The higher IGF-I will stimulate growth, while the higher insulin will promote glucose uptake by tissues other than the udder. Cows with higher insulin concentrations in the *post partum* period therefore tend to make less milk.

We have completed two studies investigating the relationship between fertility and metabolic status in primiparous cows. The first included 188 animals kept on 6 farms. The second included 102 cows on one farm for which we had previously collected information on growth rate and fertility as maiden heifers. Reproduction in all animals was closely monitored using milk progesterone profiles and animals were blood sampled at strategic intervals both before and in the 7 week period after calving to assess metabolic hormone levels. Body condition score data were collected over the same period in both studies and in the second study cows were also weighed at weekly intervals.

Despite their apparently more favourable metabolic profiles in terms of reproduction, primiparous cows on average exhibit slightly poorer fertility than their older counterparts (Table 2). The most notable difference is an increased likelihood of experiencing a long delay in the resumption of ovarian cyclicity, with about 21% experiencing a significant delay to first ovulation (>45 days) in comparison with only 9% in older cows. Interval to conception was similar in primiparous and multiparous cows which did conceive, but a slightly higher proportion of primiparous animals failed to conceive at all.

Table 2. *A comparison of fertility parameters in primiparous and multiparous cows.*

Fertility parameter	n	Primiparous	n	Multiparous
Days to first progesterone rise	188	28.5 ± 1.37	305	26.8 ± 1.05
No. with delayed ovulation (>45 days)	39	21% [a]	29	9% [b]
Days to 1st service	180	78.5 ± 2.42[a]	294	72.9 ± 1.12 [b]
Days to conception	151	93.9 ± 5.35	266	95.7 ± 2.27
Services/conception	151	1.6 ± 0.09	262	1.9 ± 0.08
No. which failed to conceive	39	21%	48	16%

Values are mean ± sem. Within rows, a>b P< 0.05

In this paper we focus on two aspects of fertility, interval to conception and failure to conceive during the service period. In the first study the metabolic characteristics of animals at different intervals pre- and *post partum* were related to interval to conception using the ASREML modelling programme (restricted maximum likelihood). This revealed a changing pattern over time. Pre-calving the most influential traits were BCS and urea. In both cases the relationships were positive, These two traits remained a significant influence on conception interval until 7-8 weeks *post partum* (the start of the service period). By then, however, the relationship with BCS was negative. This showed that animals calving with a higher BCS subsequently suffered a greater loss of condition and took longer to conceive. Although there was a trend towards higher peak milk yields in cows with longer conception intervals (Table 3), inclusion of peak milk yield in the model did not achieve statistical significance. Animals which failed to conceive at all had similar milk yields to the rest of the animals on the study (31.6 ± 0.40 kg, n = 148 v 31.6 ± 0.97 kg, n = 40) but tended to have slightly higher urea values before calving (pregnant 4.3 ± 0.22 mmol/L, n = 151, FTC 5.2 ± 0.41 mmol/L, n = 40, P < 0.07). This was consistent with the data from interval to conception, in that higher urea values pre-calving predisposed to a longer interval.

Table 3. *Comparison of the relationship between peak milk yield (PMY) and conception data in primiparous and multiparous dairy cows.*

	Primiparous		Multiparous	
Interval from calving to conception	n	PMY (kg)	n	PMY (kg)
<80 days	36	30.3 ± 0.87	67	34.9 ± 0.87[a]
80-150 days	80	31.7 ± 0.53	81	43.3 ± 0.88 [b]
>150 days	32	32.6 ± 0.82	27	48.5 ± 1.06 [c]

Values are mean ± sem . a<b<c, P < 0.01

The first study therefore showed that the condition in which a cow calved had a major influence on her reproductive performance. In the second study we investigated this further by relating condition at calving to the events leading up to this point. Both body weight and body condition score at calving were highly positively correlated with size measurements at 3-6 months.

Animals which were heavier at calving also had higher pre-calving IGF-I concentrations, and subsequently lost more weight and condition and produced more milk.

The second study also showed that cows which failed to conceive in their first lactation (13/94, 14%) had required more services to achieve a pregnancy as a maiden heifer, thus taking longer to conceive and calving for the first time when slightly older. In their first lactation they took longer to resume cyclicity, had fewer normal progesterone profiles and produced less milk. Pre-calving their body condition score, body weight and IGF-I concentrations were all significantly lower (Swali, 2005).

This shows that there is an optimum condition in which to calve. Fertility problems of two types may arise in the first lactation. Higher genetic merit cows tend to grow well as youngstock, conceive early as heifers, calve relatively young and then go on to produce more milk. This is produced at the expense of a higher rate of condition score loss in early lactation which is associated with a reduction in fertility. In addition, if such animals are overconditioned at calving, they will have an increased incidence of dystocia which also impairs subsequent fertility (Roy, 1990). These animals do, however, generally conceive eventually. At the other extreme we have identified another group of animals which grew poorly, had worse fertility as heifers and calved both older and at a lower weight than their compatriots. These produced less milk and failed to conceive again. We do not yet know the extent to which these problems are caused by genotype or environment (eg enteric or respiratory infection) during their earlier development.

Multiparous cows

Animals which have reached their second lactation are by definition already selected on the basis of adequate fertility as juveniles and low-producing animals are also likely to have been culled out. Multiparous cows have reached mature body weight and increased their capacity for milk production beyond that reached in the first lactation. In comparison with primiparous cows, both insulin and IGF-I concentrations are significantly lower, falling to very low levels in the 2 week period following calving (Wathes et al. 2001; Taylor et al. 2004a). Using the same ASREML modelling approach to that outlined above revealed a somewhat different pattern of metabolic hormone changes over time associated with longer calving to conception intervals than that found in the primiparous cows. In this case the leptin, NEFA and urea values pre-calving were all influential, with longer intervals associated with higher leptin and lower NEFA and urea concentrations. In the immediate *post partum* period fertility was most strongly predicted by the IGF-I concentration, with cows reaching lower concentrations taking longer to conceive. By the start of the service period the most influential factors in our analysis were urea and BCS. In this case the relationship with urea was positive so that higher urea values were associated with longer intervals. In contrast to the primiparous cows, inclusion of peak milk yield in the model was highly significant (see Table 3).

As with the younger animals we also analysed the data from multiparous cows which failed to conceive (48/305 or 16% of cows on this study). These showed a different metabolic profile, indicating that they represent a distinct population. In this case they were characterised by lower urea concentrations both before and after calving. This is likely to be indicative of an underlying metabolic problem but the precise mechanism linking it to infertility remains uncertain.

There are two schools of thought over interpretation of urea data in relation to fertility. On the one hand, urea concentrations reflect ammonia production in the rumen and there are suggestions that high concentrations may be directly toxic to the gametes and cause elevated and potentially harmful pH values in the reproductive tract (Butler, 1998). On the other hand, arguments have been made than a higher urea value reflects an imbalance between protein and available energy in the diet and is another sign that cows with higher urea values are in worse negative energy deficit (Laven and Drew 1999). Whilst both are probably true to some extent, our own data support that latter hypothesis as being the most likely explanation for the link found in our study. The urea values recorded rarely exceeded the range above which toxic effects are thought to occur (about 7mmol/l, Butler, 1998) The higher genetic merit animals consume more protein and convert it into milk, using stored body energy in the process. Once again cows in greater energy deficit will have more difficulty in conceiving.

Conclusion

The trend towards reduced fertility in the past 40 years is associated with higher milk production, but other management factors are also important contributors. In particular, a variety of diseases experienced on farms can depress both fertility and yield. The changes in metabolic status at the onset of lactation place the cow into a state of negative energy balance (NEB). The depth and length of NEB tend to be higher in higher producing animals in which genetic selection has favoured the increased mobilisation of body tissues to provide energy to support yield. The precise signals which relate NEB to reduced fertility are complex and remain to be fully unravelled. Of the factors currently measured, IGF-I and urea appear to be the most strongly related to fertility. However, in neither case is the relationship straightforward as it changes both with age of the animal and stage of the lactation. This in part explains the generally poor correlation between many metabolic measures and fertility in which these time-related changes are often ignored. Body condition score remains a useful guide as it can be undertaken directly on the farm and can be used to determine the rate of tissue mobilisation in early lactation. Available data show that it is particularly important for a cow to calve in an appropriate condition score, as both extremes of condition will place the animal at a metabolic disadvantage immediately after calving from which it will take a considerable time to recover. The metabolic status and thus fertility at the start of one lactation will be influenced by events during the rearing period and in the preceding lactation. We need to establish a better understanding of how the links between growth, milk production and reproduction alter as cows mature as genetic selection to promote production at one stage (eg first lactation) may not be conducive to optimising overall lifetime performance.

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References

Beam, S.W. and W.R. Butler. 1999. Effects of energy balance on follicular development and first ovulation in postpartum dairy cows. J. Reprod. Fert. Suppl. 54: 411-424.

Butler, W.R. 1998. Review: Effect of protein nutrition on ovarian and uterine physiology in dairy cattle. J. Dairy Sci. 81: 2533-2539.

Dawson, L.E.R. and A.F. Carson. 2004. Management of the dairy heifer. Cattle Practice 12: 181-192.

Durr, J.W., H.G. Monardes, R.I. Cue and J.C. Philpot. 1997. Culling in Quebec Holstein herds. 2. study of phenotypic trends in reasons for disposal. Can. J. Anim. Sci. 77:601-608.

Esslemont, R.J. and M.A. Kossaibiti. 1997. Culling in 50 dairy herds in England. Vet. Rec. 140:36-39.

Garnsworthy, P.C. and J.H. Topps. 1982. The effect of body condition of dairy cows at calving on their food intake and performance when given complete diets. Anim. Prod. 35:113-119.

Hayliri, A., R.R. Grummer, E.V. Nordheim and P.M. Crump. 2002. Animal and dietary factors affecting feed intake during the prefresh transition period in Holsteins. J. Dairy Sci. 85:3430-3443.

Kadokawa, H., D. Blache, Y. Yamada and G.B. Martin. 2000. Relationships between changes in plasma concentrations of leptin before and after parturition and the timing of first post partum ovulation in high producing Holstein dairy cows. Reprod. Fert. Dev. 12: 405-411.

Laven, R.A. and S.B. Drew. 1999. Dietary protein and the reproductive performance of cows. Vet. Rec. 145: 687-695.

LeRoith, D., C. Bondy, S. Yakar, J.L. Liu and A. Butler. 2001. The somatomedin hypothesis: 2001. Endocr. Rev. 22:53-74.

Lucy, M.C. 2001. Reproductive loss in high-producing dairy cattle: Where will it end? J. Dairy Sci. 84: 1277-1293.

Lucy, M.C. H. Jiang and Y. Kobayashi. 2001. Changes in the somatotrophic axis associated with the initiation of lactation. J. Dairy Sci. 84: E113-E119.

Mann, G.E, G.E. Lamming, R.S. Robinson and D.C. Wathes. 1999. The regulation of interferon-tau production and uterine hormone receptors during early pregnancy J. Reprod. Fert. Suppl. 54: 317-328.

Margerison, J. 2004. Review of dairy heifer rearing and its effect on performance, longevity costs and farm income. Dairying, ed E. Kebreab, J. Mills and D.E. Beever. Pp 1-36. BSAS Publication 29, Nottingham University Press.

National Research Council. 1989. Nutrient requirements of dairy cattle. National Academy Press, Washington DC.

O'Callaghan, D., J.M. Lozano, J. Fahey, V. Gath, S. Snijders and M.P. Boland. 2001. Relationships between nutrition and fertility in dairy cattle Br. Soc. Anim. Sci. Occasional Publication 26: 147-160.

Opsomer, G., M. Coryn, H. Deluyker and A. de Kruif. 1998. An analysis of ovarian dysfunction in high yielding dairy cows after calving based on progesterone profiles Reprod. Dom. Anim. 33: 193-204.

Pryce, J.E., G. Simm and J. Robinson. 2002. Effects of selection for production and maternal diet on maiden heifer fertility. Anim. Sci. 74:415-421.

Pryce, J.E.., M.D. Royal, P.C. Garnsworthy and I.L Mao. 2004. Fertility in the high-producing cow. Livestock Prod. Sci. 86:125-135.

Roy, J.H.B. 1990. The calf. 5th ed, Vol. 1, Management of Health. Butterworths, London.

Royal, M, G.E. Mann and A.P.F. Flint. 2000. Strategies for reversing the trend towards subfertility in dairy cattle. Vet. J. 160: 53-60

Sejrsen, K., S. Purup., M. Vestergaard and J. Foldager. 2000. High body weight gain and reduced bovine mammary growth: physiological basis and implications for milk yield potential. Dom. Anim. Endocrinol. 19:93-104.

Swali, A. 2005. Early development and subsequent metabolic and reproductive parameters in the Holstein-Frisian dairy calf. PhD Thesis, University of London, UK.

Taylor, V.J., D.E. Beever and D.C. Wathes. 2004a. Physiological adaptations to milk production that affect the fertility of high yielding dairy cows. Dairying, ed E. Kebreab, J. Mills and D.E. Beever. Pp 37-72. BSAS Publication 29, Nottingham University Press.

Taylor, V.J., Z. Cheng, P.G.A. Pushpakumara, D.E. Beever and D.C. Wathes. 2004b. Realtionships between the plasma concentrations of insulin-like growth factor-I in dairy cows and their fertility and milk yield. Vet. Rec. 155:583-588.

Whitaker, D.A., J.M. Kelly and S. Smith. 2000. Disposal and disease rates in 340 British dairy herds. Vet. Rec. 146: 363-367.
Wathes, D.C., V.J. Taylor and Z. Cheng (2001) Metabolic interactions with fertility Cattle Practice 9: 291-296.

Wathes, D.C., V.J. Taylor, Z. Cheng and G.E. Mann. 2003. Follicle growth, corpus luteum function and their effects on embryo development in the post partum cow. Reproduction Supplement 61: 219-237.