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Genetics and genomics of fertility in dairy cows

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ABSTRACT

The existence of significant and sufficient genetic variation in fertility is generally accepted and most leading dairy cattle breeding programmes have included fertility in their selection indices (Miglior and others 2005). This multi-trait selection has been very effective and reversed the negative genetic trend for fertility. Selection is based on traits derived from calving dates and insemination dates. These traits are biased by farm management decisions, whereas endocrine fertility phenotypes reflect a cow's physiology directly and are thus better than fertility traits for animal breeding. Genomic selection (Meuwissen and others 2001) predicts breeding values for a large number of genetic markers across the entire genome. Genomic selection will improve the rate of progress for the fertility traits. Current developments include the use of whole genome sequence information, with the prospect of using the causal mutations for selection, and the use of in-line progesterone measures to develop better fertility traits. For the future this holds the promise that farmers should spend less money, treatments and labour to achieve optimal fertility for their herd, since the genetic potential for fertility will improve due to more effective selection.

GENETICS OF FERTILITY

The existence of significant genetic variation in fertility is generally accepted (Pryce and Veerkamp 2001, Flint 2006, Rydhmer and Berglund 2006). Heritability for fertility traits commonly used in animal breeding is relatively low, due to the large unexplainable residual variation in statistical models trying to predict traits like calving interval and pregnancy rate at the individual cow level. The existence of strong genetic effects are evidenced by differences in mean calving interval of up to 30 days between daughters of different sires. Similarly, the difference in pregnancy rate between daughters of extreme Holstein sires is as high as 7%, which equates to roughly 29 days open per lactation (Weigel 2006).

There is also overwhelming evidence that increasing genetic merit for yield without considering genetic merit for fertility, reduces fertility (Pryce and Veerkamp 2001, Veerkamp and others 2003). Over the previous two decades the interval from calving to conception increased by 24 days in the US (Shook 2006). Illustrative of this trend, Holstein herds in south-eastern states reported increases in average days open of 40d and over between 1982 and 1999, whilst conception rates decreased from about 50% to 34%. Unfavourable genetic changes in conception interval since 1980 accumulated to 1.0 genetic standard deviations and genetics has been estimated to account for one-third of the decline in pregnancy rate (Shook 2006).

To date, none of the leading dairy cattle breeding programmes select on yield only, and by using multi-trait selection they have included fertility in their selection indices (Miglior and others 2005).

This multi-trait selection has reversed the negative genetic trend in most countries. For example, in the Netherlands (Figure 1) the genetic potential of cows showed a steady decline, *e.g.* genetic potential for interval calving - first insemination increased by 15 days before the millennium, but since the introduction of fertility indices this genetic trend levelled off and is improving again. Similar patterns are observed for the other fertility traits. The most limiting factors for even faster genetic progress for fertility are the genetic association between fertility and yield, the low accuracy of breeding values due to poor recording, and the long generation interval.

ASSOCIATION BETWEEN MANAGEMENT, YIELD AND FERTILITY

The impact of these genetic trends depends greatly on the changes in farming management and other practices like fertility diagnosis and heat detection. Are these able to compensate for the declining genetic potential? The observed phenotypic trend may in fact be higher or lower than the genetic trend depending on influences by management and nutrition. In Figure 2 we show that for calving interval it was not possible (or desirable) to compensate the unfavourable genetic trend within the practical and economic constraints of daily management. Calving interval increased by 25 days between 1995 and 2010, which is double the genetic trend that showed an increase in calving interval of 10 days. Although these numbers are on a different scale (cows born and cows milking) it seems to suggest that calving interval has decreased more than could be expected from the

Figure 1. Development of the genetic merit of dairy cows over the past decades for fertility traits: interval calving - first insemination (I_FS), interval first service - last service (I_FS_LS), calving interval (CIV) and percentage none return after 56 days.

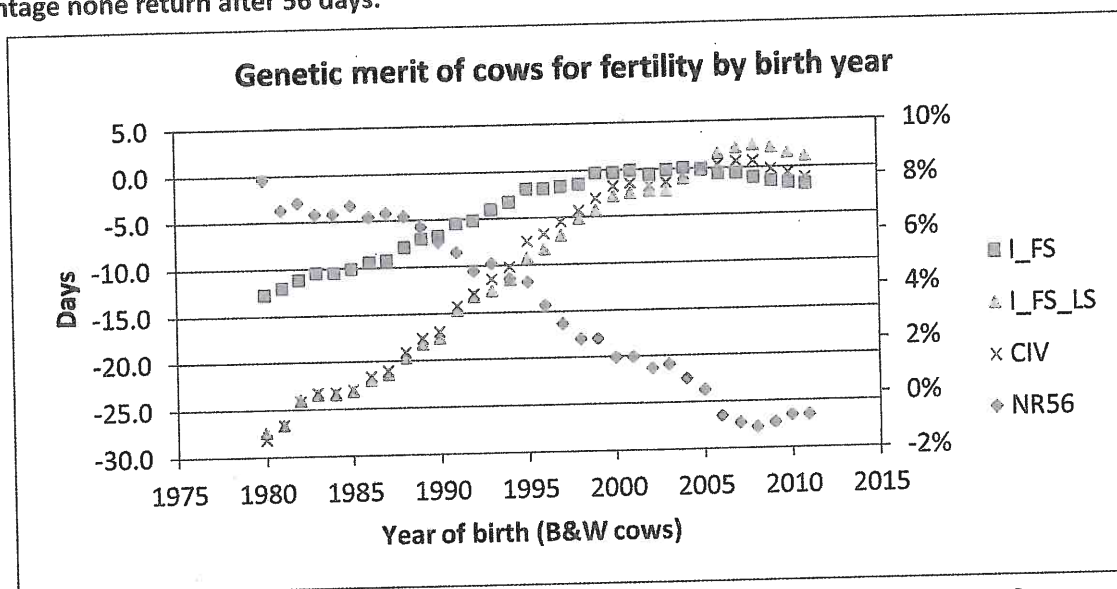
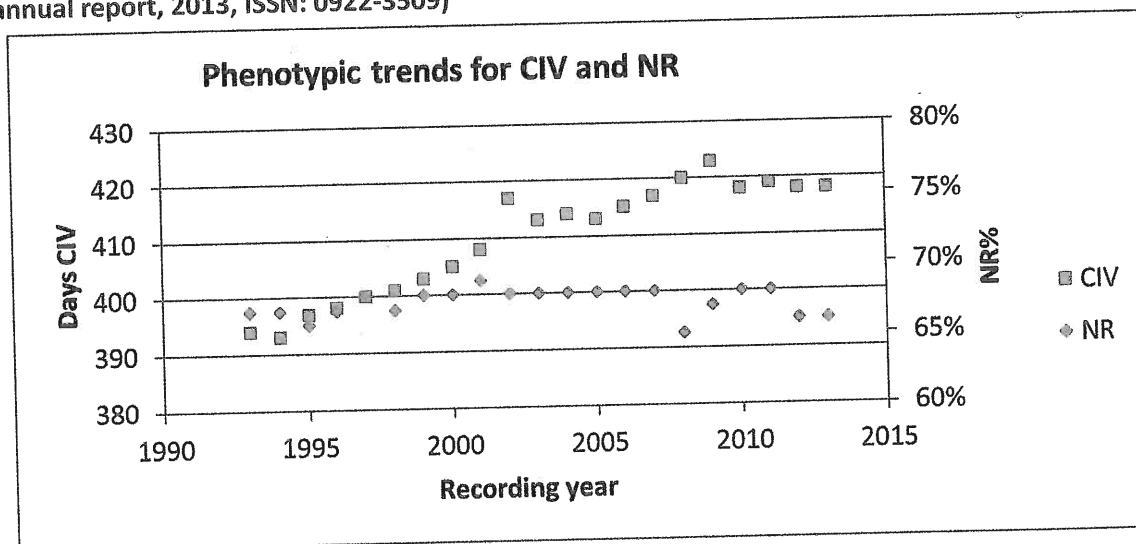


Figure 2. Phenotypic trend for calving interval (CIV) and percentage none return after 56 days (NR) (source: CRV annual report, 2013, ISSN: 0922-3509)

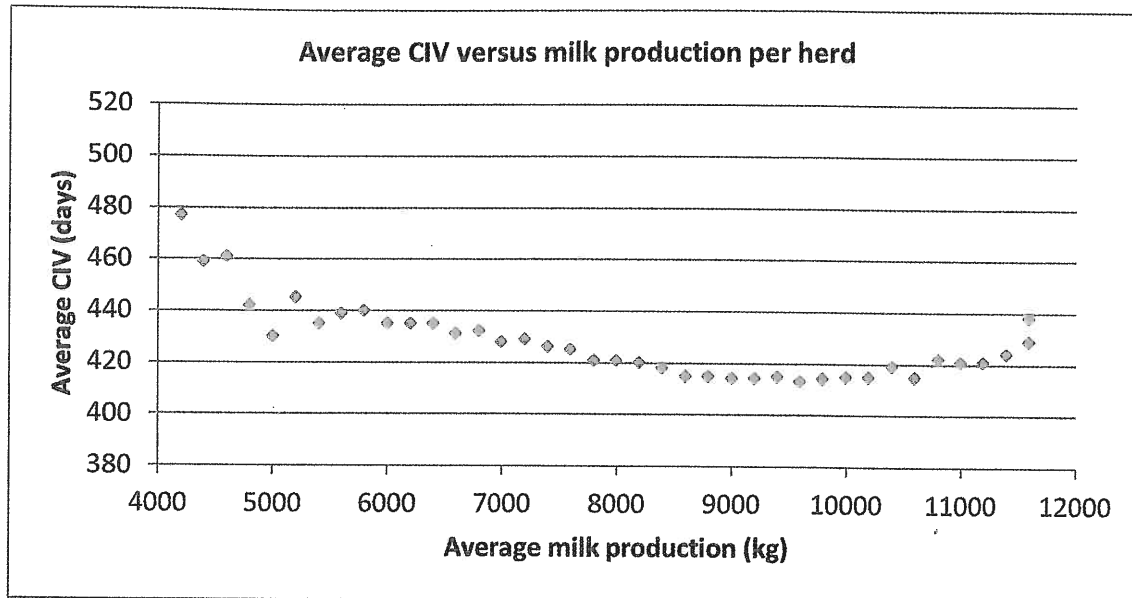


genetic trend alone. Conversely, for percentage none return after 56 days we saw till recent a clear negative genetic trend, but no phenotypic trend. It might well be that the poorer genetic potential of cows for pregnancy rate is compensated by improvements in semen quality.

Thereby, it is important to note that the association between milk production and fertility varies from herd to herd, both phenotypically (Windig and others 2005) and genetically (Windig and others 2006). For example, the strength of negative associations between yield and fertility is equal to or lower in high production herds compared to low production herds (Castillo-Juarez and others 2000, Kearney and others 2004, Oltenuacu and Algers 2005). Also, in one of our experiments (Windig and others 2008) milk

progesterone profiles were determined from samples obtained twice weekly for 100d postpartum in 100 Holstein primiparous cows. Three treatments were applied in a 2x2x2 factorial arrangement with high-low genetic merit for overall production, high-low caloric density diet, and 2-3 times milking/day as factors. Interestingly, high genetic merit and three times a day milking caused a delay of 10 and 7 days in days till first luteal activity; no effect due to the diet was observed although all three treatments had an effect on milk yield. This is also what is observed across Dutch herds (Figure 3), there is no association between the level of milk production and calving interval. All these conflicting results indicate that sometimes there is an association between milk production and fertility, and sometimes none, but also that there is no

Figure 3. Association between herd production level (kg milk per lactation) and calving interval (CIV) (source: CRV annual report 2013, ISSN: 0922-3509)



clear causal relationship between phenotypic yield and fertility. The reduced fertility due to selection for yield is not necessarily a consequence of the increase in yield *per se* (Gutierrez and others 2006, Weigel 2006). Different mechanisms may underlie the clear negative genetic correlation between yield and fertility, *e.g.* pleiotropic gene effects, linkage or complex physiological associations (Veerkamp and others 2003). Also, genetic selection for yield may change the energy partitioning in lactating dairy cows, causing a genetically induced negative energy balance and a lower body condition score (Veerkamp and others 2003, Gutierrez and others 2006), *i.e.* states associated with poor fertility. Because there is no causal relationship between fertility and yield, and genetic associations between yield and fertility are below unity (Royal and others 2002, Andersen-Ranberg and others 2005, Jamrozik and others 2005) conjoint selection for milk yield and reproductive performance is possible whilst maintaining 70 to 80% of the yearly increase in yield (Veerkamp and others 2000). This possibility is also confirmed by the genetic trend in the Netherlands (Figure 1).

GENOMIC SELECTION

Since the availability of molecular techniques to determine variation between animals at DNA level such as micro-satellites, restriction fragment length polymorphism (RFLP), single nucleotide polymorphism (SNP), there has been an interest in utilising this information in selection, and several experiments identifying genetic markers for functional traits have been performed. However, the identification of variation in genes that are

involved directly in regulating traits of interest has proved to be time consuming and costly, with few successes in terms of practical applications so far.

The recording of SNP spread across the genome of different species and the opportunity to genotype individual animals for many tens of thousands SNPs opens up possibilities to include genome-wide marker information for predicting breeding values. Genomic selection (Meuwissen and others 2001) predicts breeding values for a large number of SNPs across the entire genome. Compared to traditional breeding practice, including such information yields a considerable increase in selection response for juvenile animals that do not have phenotypic records, and potentially can reduce the costs of a breeding programme up to 90% (Schaeffer 2006). In 2006, cooperative cattle improvement organisation CRV announced the implementation of genomic selection in dairy cattle using 3000 SNPs at that time. To date all major dairy cattle breeding companies have implemented genomic selection programmes, and additional rates of gain of 60% are observed.

However, the accuracy of genomic breeding values does not approach unity yet, despite using reference populations of tens of thousands of animals to estimate the SNP effects. Also, predicting genomic breeding values across populations is not yet sufficiently accurate. To achieve better genomic predictions it is important that functional mutations for QTL with low minor allele frequencies are also detected. Therefore, to date the use of whole-genome sequence information in genomic breeding is explored, and the complete genome for more than a 1000 bulls is known (<http://>

www.1000bullgenomes.com/). Since many of today's bulls are descendants of these sequenced founders or share chromosome segments with these bulls, we have been able to impute the whole chromosome of about 5000 of today's bulls. This will aid the research into genetic differences for fertility, and hopefully increase the accuracy of genomic prediction even further.

NEW FERTILITY TRAITS

The low heritability for classical fertility ($h^2 < 0.1$) may be explained by the fact that classical fertility traits are highly influenced by farm management decisions and poor recording practices (Hayes and others 1992, Campos and others 1994, Marti and Funk 1994). For instance, a planned extended calving interval (CI) will delay the interval from calving to first service (CFS), not because a cow has a late start of cyclic activity, but because of the farmer's decision. Thus, this constrains efforts to improving fertility by selection. These constraints can be minimised by using fertility traits with higher heritability or exploiting genomic information.

Endocrine fertility traits have been suggested as alternative indicators for fertility in dairy cows because they more directly reflect a cow's physiology, and have higher heritability (Bulman and Lammings 1978, Darwash and others 1997, Lammings and Darwash 1998, Darwash and others 1999).

As part of the RobustMilk project we utilised data on primiparous Holstein-Friesian cows from experimental farms in Ireland, the United Kingdom, the Netherlands and Sweden to identify genomic regions associated with classical measures of fertility, as well as an endocrine fertility phenotype derived from milk progesterone profiles, *i.e.* calving to first luteal activity (CLA). Heritability estimates of the classical fertility traits varied from 0.03 to 0.16; the heritability for CLA was 0.13. The results from this study (Berry and others 2012) suggested also that the power of genome-wide association studies in cattle may be increased by using endocrine measures of the trait under investigation.

The application of milk progesterone (P4) in routine genetic evaluation schemes has been constrained by the high cost associated with collecting these measures in sufficient samples per cow. Until recently, methods to measure milk P4 level were manual and labour intensive. However, P4 level measuring technology has advanced to allow in-line systems to instantly measure milk P4 level (Friggens and others 2008), and several farmers have installed this Herd Navigator system

of DeLaval. In these in-line P4 records systems, milk is automatically sampled, P4 level measured, and recorded. Using data from 14 farms in the Netherlands (Tenghe and others 2014). We defined several endocrine traits: a) days to commencement of luteal activity, b) days from commencement of luteal activity to first service, c) luteal activity during first 60 days in milk, d) Proportion of samples with luteal activity, e) length of first luteal phase, f) Length of first inter-luteal interval and g) length of first inter-ovulatory interval. The last two endocrine traits showed no genetic variation, but the traits commencement of luteal activity, interval from commencement of luteal activity to first service, and proportion of samples with luteal activity showed a higher heritability as compared to the classical fertility traits calving interval and period between calving and first insemination. These higher heritabilities are due to the more accurate measurement and the frequency of measuring, and offer opportunities for breeding as the breeding values for these new fertility traits are more reliable.

CONCLUSION

New technologies enhance genetic selection for fertility as they can provide valuable routinely measured endocrine fertility phenotypes, accurate genotype effects for genomic prediction to enable selection at a young age, and might lead to discovery of causal mutations. For the future this holds the promise that farmers should spend less money, treatments and labour to achieve optimal fertility for their herd, since the genetic potential for fertility will improve due to more effective selection.

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