Can Genomics be Used to Improve Reproductive Performance?

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Take Home Messages

- Fertility is an essential component of efficient dairy production. Although fertility traits are strongly influenced by the environment, new evidence supports genetic variability related to multiple reproductive traits, providing opportunity for selection.
- Identifying genomic variation associated with specific fertility measures, such as uterine health, resumption of postpartum ovulation, and establishment and maintenance of pregnancy in cows, would result in a wider understanding of the genetic structure of reproduction.

The Context

Dairy production systems face the challenge of increasing the efficiency of milk production, while minimizing environmental impact and ensuring the welfare of animals (Maltecca, 2013). In this context, adequate fertility is one of the critical factors for achieving this goal.

Poor reproductive performance results in low proportions of cows at their peak production period, higher insemination costs, and delayed genetic progress (Norman et al., 2009; Santos et al., 2010). Moreover, impaired fertility has been reported as one of the most frequent reasons for culling (Pinedo et al., 2010) and increased days open (DO) are associated with a greater risk of death or culling in the subsequent lactation (Pinedo and de Vries, 2010).

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As extensively reported, a historical trend of declining dairy fertility has been evident in multiple countries and regions, under diverse production systems (Lucy, 2001; VanRaden et al, 2004; Walsh et al., 2011). Worsened fertility has resulted from high prevalence of anovulation, reduced fertilization, and embryonic survival (Santos et al., 2004; 2009), likely related to changes in cow physiology, greater levels of inbreeding, nutritional management, housing, increased herd size, reduced estrus expression, and current genetic makeup (Lucy, 2001; Weigel, 2006).

Starting in the fifties, breeding programs selecting for milk production have been very successful and current trends indicate increments on milk yield per cow of 1 to 2% per year (Rauw et al., 1998; Bello et al., 2012). However, some unfavorable genetic correlations between production and other traits may exist, resulting in undesirable side effects, such as a higher risk for behavioral, physiological, and immunological problems (Hansen et al., 1983).

Although these negative associations between production and fertility traits are probable (Norman et al., 2009; Bello, 2012), it is possible to select for improved milk yield and fitness traits, including fertility. This fact is, at least in part, evidenced by 2003 genetic evaluations of daughter pregnancy rate (DPR) which showed increments in reproductive performance in Holsteins (Norman et al., 2009). The trend for DPR indicates a partial recent recovery in dairy fertility, despite no apparent slowing down in the rate of increase of milk production per cow. As shown in Figure 1, the trend for lower DPR values in the U.S. dairy herd has now reverted.

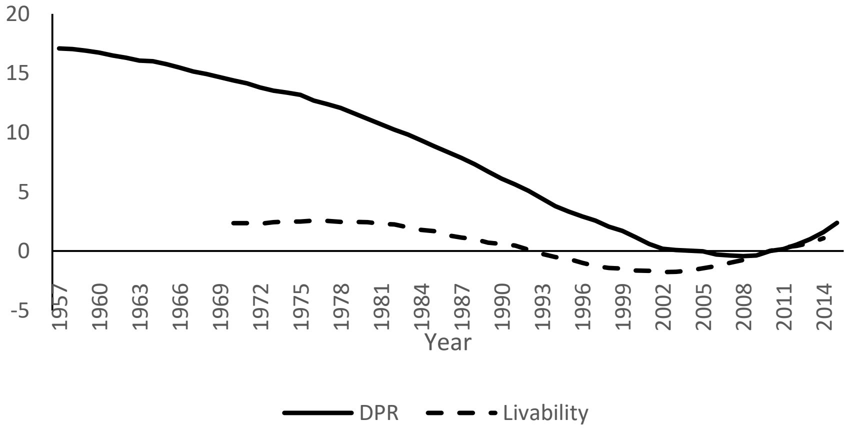

Figure 1: Trends for daughter pregnancy rate (DPR) and livability for US Holstein cows. Adapted from Council on Dairy Cattle Breeding (https://www.uscdcb.com/)

▪ Genetics and Fertility

Fertility traits have a multi-factorial nature, which makes it difficult to determine the degree of involvement of genetics on reproductive outcomes. Genetic variation may be directly involved in the physiology of reproductive processes. However, genetics may also determine, to some extent, the behavior of other related traits that have an impact on fertility. Among others, these comprise the ability to maintain an adequate body condition and DMI during the transition period, the potential for adequate immune responses resulting in adequate health, and the capacity to retain early pregnancy (Walsh et al., 2011; Ferguson and Skidmore, 2013).

It has been established that reproductive traits are polygenic and largely influenced by the environment (Holmberg et al., 2006). Consequently, genetic progress for fertility, by way of conventional breeding strategies, is hindered by low heritability, which represents the proportion of phenotypic variation attributable to genetic differences among animals (Norman et al. 2009). Moreover, high costs of large data collection, the long time period required for data validation, and the potential for biased phenotypes, such as non-return rates and DPR, are significant obstacles (Schnabel et al., 2005). Adding to these limitations, the influence of factors unrelated to fertility, such as breeding policy and voluntary waiting period, is a constant difficulty for precise reproductive estimations.

Several authors have reported heritabilities below 0.10 for reproductive performance traits (Hansen et al., 1983; VanRaden et al., 2004). Yet, when more objective measures of fertility were evaluated (interval to first ovulation, anovulation, and pregnancy loss), heritabilities were moderate to high (0.16 to 0.48; Darwash et al., 1997; Bamber et al., 2009). For reproductive disorders, such as metritis and retained placenta, heritability estimates were close to 0.20 (Zwald et al., 2004). Notably, genetic variation is manifest when DPR is considered, as daughters of the highest and lowest sires for DPR (differing by 7.2% in DPR) differ by 29 d open per lactation.

▪ Genomic Selection of Dairy Cattle

With the sequencing of the bovine genome and the arrival of low cost genotyping of large numbers of single nucleotide polymorphisms (SNP) markers, the use of DNA analysis in the evaluation of dairy cattle genetics has become a reality (Wiggans et al., 2012). Genomic evaluations have been implemented in the United States, Canada, Great Britain, Ireland, New Zealand, Australia, France, the Netherlands, Germany, and the Scandinavian countries (Weller et al., 2017). From a logistics point of view, the use of genomic analyses allows for the estimation of breeding values at birth, which reduces the costs of proving bulls and increases the genetic gain because of shorter generation intervals (Schaeffer, 2006). In addition, genotyping platforms commercially available from several companies have become widely used at the farm level, particularly for genotyping of females.

As with genetic evaluations, genomic selection has not been restricted to production characters. Other traits of economic interest, such as Productive Life, Net Merit, etc. (Ashwell et al., 2004), have been integrated and evaluations have subsequently expanded to more specific health problems. Although genetic selection is an attractive tool for improvement of health traits, contrary to production traits, fitness and health present additional challenges associated with the inconsistency of recording systems and moderate to low heritabilities (Parker Gaddis et al., 2014; Zwald et al., 2004).

In the US, indirect health predictions are available from the Council on Dairy Cattle Breeding and recent data indicate that these traits result in genetic improvements for resistance to adverse health events (McNeel et al., 2017; Vukasinovic et al., 2017). Producer-recorded health events have been successfully used to identify genetic differences between dairy sires in daughter susceptibility to common health disorders, including metritis, displaced abomasum, and mastitis (Zwald et al., 2004; Parker Gaddis et al., 2014).

At the present, genomic evaluations estimating the genetic risk for 6 specific health events in US Holstein dairy cattle have been developed (Vukasinovic et al., 2017). Wellness trait predictions include genetic predictions for retained placenta, metritis, ketosis, displaced abomasum, mastitis, and lameness.

▪ Genomic Selection for Fertility

Specific reproductive traits that are currently evaluated by genomic analyses in the US include daughter pregnancy rate (%), sire calving ease, daughter calving ease, sire stillbirth rate (%), daughter stillbirth rate (%), heifer conception rate (%), and cow conception rate (%).

New research exploring genomic variation related to novel fertility traits is in course. Two main approaches have been developed to determine associations among genetic markers and fertility: the candidate gene approach and the whole genome scan (Veerkamp and Beerda, 2007). As a result, a number of areas of the genome affecting quantitative traits that are governed by multiple genes (known as quantitative trait loci; QTL) for cattle reproductive traits have been mapped. Initial QTL studies used a family structure design with hundreds of markers revealing large linkage regions. More recently, genome-wide association studies (GWAS) performed with thousands of SNP markers have facilitated the resolution of associated regions and the discovery of candidate genes (Matukumalli et al., 2009).

Quantitative trait loci have been identified for many reproductive traits including ovulation rate (Gonda et al., 2004), pregnancy rate (Ashwell et al., 2004; Muncie et al., 2006), DPR (Schnabel et al., 2005), non-return rate, estrus intensity, and calving performance (Holmber and Andersson-Eklund, 2006; Jemaa et al., 2008). Genetic variation has also been identified for gestation length (Schrooten et al., 2000), dystocia and stillbirth (Kuhn et al., 2003).

In addition, genomic analyses have offered the capability to locate lethal genes affecting fertility outcomes; VanRaden et al. (2011) identified five new fertility defects in dairy breeds by examining specific genomic areas that had a high population frequency but were never homozygous. These lethal effects may result in conception, gestation, and stillbirth losses.

As stated previously, some physiological measures of fertility (e.g. resumption of estrous cyclicity after calving, anovulation) have moderate heritabilities; this is also the case for some reproductive disorders (Zwald et al., 2004). Interestingly, it has been established that cows that resume estrous cyclicity soon after calving are more likely to show estrus and to become pregnant in a timely manner. Similarly, healthier cows are advantageously able to conceive sooner after parturition.

Therefore, decomposing aggregate reproductive phenotypes into their detailed components, which are potentially less influenced by management, could prove to be more heritable and, assuming sufficient genetic variation exists, genetic gain for reproductive performance could be accelerated (Carthy et al., 2014). For example, DPR is a function of DO, calculated from a theoretical 60-day voluntary waiting period, which is highly sensitive to breeding policy (voluntary waiting period, use of timed A.I., and use of bull breeding). Another traditional reproductive measure, calving interval, is composed of several reproductive components, such as the postpartum interval to commencement of estrus cyclicity, expression of estrus, conception, maintenance of pregnancy, and gestation length (Carthy et al., 2014).

Presently, a major goal to advance genomic selection for fertility is the collection of high numbers of accurate fertility phenotypes associated with the corresponding genotypes, coupled to large scale evaluations of the aforementioned direct measures of fertility. A subsequent step should aim at the identification of genomic regions with large- to moderate-effects on the quantitative traits of interest. Collecting accurate data represents another challenge and potential strategies may include using DHI and data recorded within on-farm herd management software programs.

Regarding the use of assisted reproductive technologies, from the perspective of embryo production efficiency, SNPs associated with the number of viable oocytes, fertilization, cleavage and developmental rates have been recently explored. Specific genotypes had variable fertilization and embryo development rates (Khatib et al. 2008; Cochran et al., 2013), demonstrating the potential interest of genomic selection applied to embryo technologies. In connection with this point, several studies predicted that new reproductive technologies, such as embryo transfer and multiple ovulation, would have a major effect on genomic selection. In recent years, A.I. organizations have begun using in vitro fertilization (IVF) heavily and selecting embryos for implantation based on genotype, which should reduce the age of donors, as well as the generation interval along the sire-to-bull pathway by up to 7 months (Weller et al., 2017; Wiggans et al., 2017).

Selection for traits with low heritability could be integrated into reproductive technologies that allow for higher rates of genetic improvement by increasing the reproduction of superior females (Parker Gaddis et al., 2017). Studies conducted in the 1980s and 1990s indicated that reproductive technologies could increase genetic gain by 10 to 20% compared with traditional breeding schemes (Ruane and Thompson, 1991).

▪ Some Comments on Our Research

Our team of researchers from different US institutions was awarded a multi-year grant to explore genomic variation associated with reproductive traits in dairy cattle (Genomic Selection for Improved Fertility of Dairy Cows with Emphases on Cyclicity and Pregnancy; Grant no. 2013-68004-20361 from the USDA NIFA). The overall objective was to develop a fertility database with genotypes and phenotypes based on objective and direct measures of fertility in Holstein cows. The subsequent goal was to identify SNPs and haplotypes significantly associated with fertility traits by use of genome-wide analyses and use this information to obtain genomic-estimated breeding values that can be applied in the selection of dairy cattle for improved fertility.

Consequently, our approach was to test a significant number of cows (approximately 12,000 from 7 States in the US) that were enrolled at calving and weekly monitored at farm until pregnancy confirmation. The evaluations included uterine health, metabolic status (subclinical ketosis) during transition, resumption of postpartum ovulation, estrus, pregnancy per A.I., and pregnancy loss, under different management practices and environments.

Our initial analyses indicated that overall, 71% of the population resumed ovarian cyclicity by 50 DIM. Conception at first and second A.I. were 32.8% and 33.7%. Pregnancy loss between 32 and 60 d after A.I. were 10% and 8.7% for first and second A.I, respectively. Overall, 19.7% and 4% of the population was sold or died before 305 DIM.

A reproductive index (RI), calculating the predicted probability of pregnancy at first A.I. (PP1) after calving, was developed using a logistic regression models that included cow-level variables that were thought to have a genetic component [diseases, anovulation, body condition score (BCS), milk yield, etc.]. Within each farm and season, cows were ranked using the developed RI as highly-fertility pregnant (850 cows) and a lowly-fertility non-pregnant (1,750 cows). The PP1 for the highest RI quartile was 0.43, while 42% of this population was pregnant at first A.I. The PP1 for the lowest RI quartile was 0.21, with 20.8% of this population pregnant. These high and low fertility subpopulations are the base for our subsequent association studies, using a high density genotyping platform (777k BovineHD BeadChip).

As mentioned before, reproductive performance is affected by multiple variables including the cow's nutritional and health status, as well as environmental factors. In this idea, we performed a sub-study (Chebel et al., 2015) within the overall project testing associations among BCS change from calving to 35 days in milk (DIM), resumption of cyclicity by 50 DIM, and both productive and reproductive performance. Holstein cows (n = 5,175) from 9 dairy herds from the Southwest, Southeast and Midwest of the U.S. were used. Cows had BCS assessed at 3 and 35 DIM and were classified according to BCS change [gained (G), no change (NC), moderate loss (ML) = −0.25 to −0.75, and extreme loss (EL) > −0.75]. Blood sampled at 7 DIM was used to diagnose ketosis (β-hydroxybutyrate; BHB >1.0 mmol/L). Calf gender, occurrences of calving problems (i.e., twins, stillbirth, and dystocia), mastitis, displacement of abomasum, and respiratory illness during the 60 DIM were recorded. Cows were milked thrice daily and average milk yield during the first 90 DIM was recorded.

Our results indicated that among cows calving with BCS <3.25, milk yield was lowest for cows gaining BCS and cows with extreme BCS loss (G = 34.4, NC = 37.1, ML = 38.2, and EL = 34.4 kg/day). Among cows calving with BCS = 3.25 to 3.5 (G = 35.4, NC = 36.3, ML = 37.9, and EL = 39.1 kg/day) and cows calving with BCS >3.5 (G = 26.0, NC = 35.0, ML = 37.5, and EL = 38.5 kg/d), milk yield was greatest when cows had extreme BCS loss from 3 to 35 DIM. Change in BCS was associated with the likelihood of cows resuming cyclicity by 50 DIM (G = 78.8%, NC = 76.4%, ML = 74.8%, and EL = 75.9%). Although BCS change was not associated with the probability of pregnancy after first postpartum A.I., pregnancy hazard ratio (independent of A.I. number) was associated with BCS change from 3 to 35 DIM [G = 1.20, NC = 1.21, ML = 1.10, and EL = referent]. In conclusion, excessive loss of BCS from 3 to 35 DIM was associated with greater milk yield, and reduced cyclicity and reproductive performance.

A second sub-study (Gonzalez-Pena et al., 2015) was completed to estimate genetic parameters of fertility indicators in dairy cattle. Measurements from a regional sub-set of 953 Holstein cows during 2 calving years were analysed.

Three fertility indicators were evaluated: (1) probability of cycling at day 45 postpartum (Pr_Cyc); (2) probability of disease diagnosis at 45 days postpartum (Pr_Sck); and (3) probability of pregnancy after 2 A.I.s (Pr_Prg). These indicators were estimated using a logistic models including the covariables of dystocia, retained placenta, BCS at 7 and 35 days postpartum (BCS7 and BCS35, respectively), and blood BHB as an indicator of subclinical ketosis. Univariate sire models, including the effects of contemporary group and lactation number, were used to estimate the genetic parameters of DO, BCS7, BCS35, Pr_Cyc, Pr_Sck, and Pr_Prg.

The percentage of cows cycling, diagnosed with at least one disease, and pregnant after 2 A.I.s were 69.7%, 14.9%, and 64.6%, respectively. The marginal probabilities indicated that cows diagnosed with dystocia, retained placenta, metritis, and mastitis were 1.7%, 6.0%, 11.4%, and 7.3% and less likely to be cycling than healthy cows, respectively.

Cows were 2.7% and 4% less likely to be cycling per unit of increase in mucus score (indicative of metritis at 7 d after calving) and BHB, respectively. The heritability estimates for Pr_Cyc, Pr_Sck, Pr_Prg, DO, BCS7, and BCS35 were 0.23, 0.29, 0.58, 0.19, 0.25, and 0.25, respectively. Our results indicated that the considered fertility traits have an important genetic component and could be used as effective indicators of fertility in breeding and management decisions.

In summary, at this point, preliminary genome wide analyses with our high and low fertility subpopulations confirm that there is potential for genomic selection in the traits of interest. This large scale evaluation will eventually be combined with current selection traits to further refine genomic selection of cattle by dairy producers.

▪ Conclusions

Fertility is a key component of modern dairy production systems. However, a trend for declining dairy fertility has been evident in diverse production systems. Although fertility traits are strongly influenced by the environment, there is evidence for genotypic variation providing an opportunity for selection, as suggested by a partial recovery in dairy fertility since the incorporation of daughter pregnancy rate into bull genetic evaluations. Current efforts are being made to collect high numbers of accurate fertility phenotypes associated with the corresponding genotypes, coupled with large scale evaluations of the association between direct measures of fertility and genomic variation on dairy cows under different management practices and environments. As the cost of genotyping decreases, the number of animals subject to genomic evaluations is expected to continue increasing. If adequate markers and causal variants for fertility traits are identified, molecular breeding values could be estimated for each trait enabling selection to proceed population-wide.

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