WHAT WE KNOW ABOUT THE GENETICS OF REPRODUCTION

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Introduction

Animal breeding and reproductive physiology have been closely related throughout the history of animal production science, because artificial insemination provides the best method of increasing the influence of sires with superior genetics to improve production traits. The addition of genetic technologies to this paradigm allows for improved methods of selecting sires and dams carrying the best genes for production and yield of edible products and resistance to diseases and parasites. However, decreasing the number of influential parents within a population also increases the risk of propagating a recessive gene that could negatively impact the species (Ghanem and Nishibori, 2009; Meyers et al., 2010). Antagonistic genotypic relationships between production traits and fertility (Johnston et al., 2009; Collis et al., 2012) suggest that care must be taken to ensure that increasing the frequency of genes with a positive influence on production does not negatively impact the fertility of the replacement females entering the herd. The use of genetic technologies to improve reproduction have been slow in domestic farm species, mostly due to the relatively low heritability of these traits (Cushman et al., 2008; Cammack et al., 2009). Among reproductive traits, those with the greatest heritability are associated with sexual maturity (Table.1), probably because these traits depend on the animal attaining a certain age, body mass or body composition (Gargantini et al., 2005; Johnston et al., 2009). The tight relationship between growth and development genes and reproductive success suggests that genetic technologies must be used with care to improve production efficiency without negatively impacting fertility, and suggest a need for genetic markers of fertility to develop selection indices that do not focus solely on production traits.

Table 1. Heritability of reproductive traits in cattle.

Trait	*Heritability*	*References*
Age at Puberty	0.14	(Snelling et al., 2012)
	0.24	(Morris et al., 2000)
Reproductive Tract Score	0.30	(Martin et al., 1992)
Yearling Uterine Horn Diameter	0.20	(Johnston et al., 2009)
Antral Follicle Count	0.44	(Snelling et al., 2012)
Age at First Calving	0.28	(Minick Bormann and Wilson, 2010)
Calving Day	0.07	(Minick Bormann and Wilson, 2010)
Follicle Diameter	0.16	(MacNeil et al., 2006)
Heifer Pregnancy Rate	0.11	(Snelling et al., 2012)
	0.21	(Doyle et al., 2000)
	0.28	(Thallman et al., 1999)
Pregnancy Rate	0.07	(MacNeil et al., 2006)
Stayability	0.15	(Doyle et al., 2000)

Choosing Replacement Heifers

The natural tendency will be to choose the oldest and largest heifers to insure that a high proportion of those heifers have initiated reproductive cycles at the start of their first breeding season. While selecting the heifers that are heaviest at weaning will increase the percentage that is pubertal at a year of age, not all of the heaviest heifers will have initiated reproductive cycles. These heifers also usually have larger birth weights and produce heavier calves, so one can quickly begin to inadvertently increase cow size in the herd by choosing the largest replacement heifers. Conversely, care should be taken when selecting for young, light-weight heifers that have reached puberty, because decreasing the age at puberty too greatly can increase the risk of a very young heifer attaining puberty and being mated by a co-pastured bull. Having a veterinarian perform a reproductive tract score 4 to 6 weeks before the start of the breeding season, can aid in selecting replacement heifers that are of moderate age and size and are pubertal. Heifers that had a reproductive tract score of 5 had a greater pregnancy rate and earlier median calving day than heifers that had a reproductive tract score of 1 (Holm et al., 2009). Heifers that had a reproductive tract score of 1 and produced a calf in their first season still had a greater risk of failing to become pregnant in their second breeding season, even with another year of growth. This suggests: (1) that the later calving date impeded their ability to initiate reproductive cycles before the breeding season or, (2) that there was something inherently wrong with the development of the reproductive tract in these heifers. It is most likely that the answer is a combination of both of these.

Repeat Breeder Cows

Cows that have failed to conceive in one or more breeding seasons can be considered to have an inherent fertility problem, because they should have had between 3 and six opportunities to conceive. Warnick and Hansen (2010) reported that there was no difference in the percentage of Repeat Breeder cows that failed to ovulate or in the percentage that conceived; however, pregnancy loss was greater in these cows compared to cows that had always produced a calf. Furthermore, an intensive characterization of the reproductive tracts of Repeat Breeder cows demonstrated that they had fewer follicles on their ovaries compared to age-matched cows that had never failed to produce a calf (Maurer and Echternkamp, 1985).

Antral Follicle Count

Antral follicle count can be used as an indicator of fertility and reproductive age in a number of mammalian species including women and cattle (Cushman et al., 2009; Mossa et al., 2012). Using trans-rectal ultrasonography a veterinarian can visualize the ovaries and count the number of fluid filled follicles present (Figure 1). Crossbred beef heifers with fewer than 15 (Low) follicles detected by ultrasonography had lower pregnancy rates at the end of a sixty day breeding season than heifers with more than 25 (High) follicles detectable by ultrasonography. This same classification also resulted in a difference in pregnancy rate and a difference in the number of inseminations per pregnancy in dairy cows. Therefore, like puberty and RTS, antral follicle count seems to be an indicator of fertility, and based on the Repeat Breeder cow results, may even be an early indicator of how these cows will perform later in life.

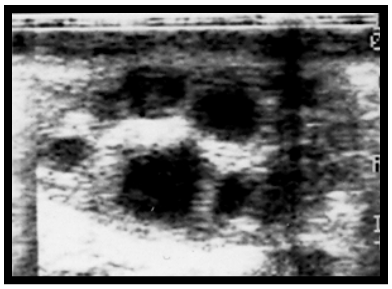

Figure 1. Ultrasound image of the ovary of a heifer with visible antral follicles (black circles). By moving the ultrasound probe across the ovary, a technician can estimate the number of follicles in the ovary.

Age at First Calving

Identifying the heifers that calve earliest may be the simplest method to improve longevity and profitability. Data from the U.S. Meat Animal Research Center collected over a 21 year period clearly demonstrated that not only did calving in the first 21 days of the first calving season result in greater herd longevity (Figure 2), but those heifers that calved early also weaned a heavier calf in each of their first 6 calving seasons (Kill et al., 2012). On average these heifers were about 2 to 3 days older than heifers calving in the second or third period. Funston et al. (2012) reported that heifers born in the first 21 days of their birth season also produced calves that were 5 to 7 days older. Thus, it is tempting to conclude that selecting older heifers will improve fertility; however, a heifer that is older at conception was probably born to a heifer that

conceived at a younger age (Minick Bormann and Wilson, 2010). Lesmeister et al. (1973) reported that the repeatability of calving period within an animal was 0.092 to 0.105, indicating that very little advancement could be made simply by selecting for those heifers that calved early in their first season. In agreement with this, calving day has a lower heritability than age at first calving (0.07 vs. 0.28) but most likely does a better job of estimating the inherent fertility of a heifer than age at first calving (Minick Bormann and Wilson, 2010).

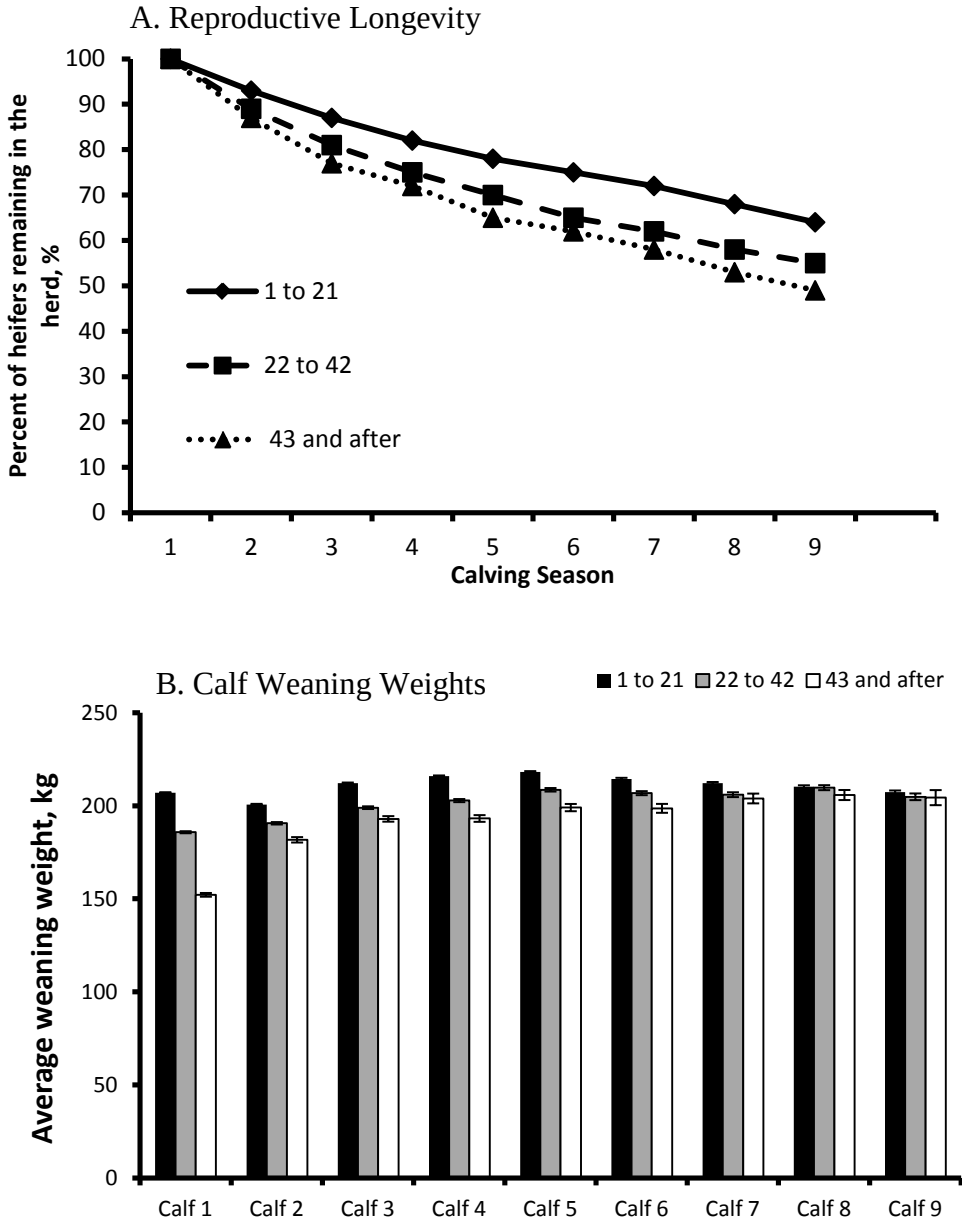

Figure 2. Influence of calving period on (A) reproductive longevity and (B) calf weaning weights at the U.S. Meat Animal Research Center. A greater percentage of animals that calved in the first 21 days as heifers remained in the herd after 5 years. These heifers also weaned a heavier calf during their first 6 calving seasons.

Limitations of These Phenotypes

Very few producers know the pubertal status of their heifers before the start of the breeding season because observing behavioral estrus is labor intensive. Palpating the reproductive tract to estimate the development or using ultrasonography to determine antral follicle number is limited by the age and size of the heifer as well as the numbers of heifers that can be processed in a day. This can range between 100 heifers if antral follicle numbers are being determined and several hundred heifers if one is simply estimating reproductive tract development. Furthermore, an ideal time to sort replacement heifers would be at weaning when they are too small to be palpated to determine development of the reproductive tract. On the other hand, most cow-calf producers know the birth date of the calves and can calculate an age at first calving for the heifers. Thus, age at first calving may become the best indicator of heifer fertility, because there are large numbers of animals available in production systems throughout the industry with this phenotype to use for discovering genetic markers of fertility. The issue remains that age a first calving is not necessarily the same trait as calving day, which may be a better estimator of inherent fertility.

Genotyping Technology

A Single Nucleotide Polymorphism (SNP) is a change in a single nucleotide in the DNA, such as a guanidine (G) to an adenine (A), that can result in a change in the amino acid sequence of the protein that is encoded by that gene. In reality, the majority of SNP are synonymous, meaning that the change in the nucleotide sequence does not result in a change in the amino acid sequence. The goal of discovery research is to identify SNP that associate with a specific trait, and can be used as genetic markers for the merit of an animal for that trait. Current technology allows for high density genotyping of the bovine genome using SNP arrays that have thousands of probes on a small chip allowing for the simultaneous genotyping of many SNPs across the bovine genome. There are commercially available bovine SNP Chips with various numbers of SNP on them depending upon the coverage of the genome that one is seeking.

Do We Need Genetic Markers of Fertility?

It is most likely that demand by the packers for certain genotypes for carcass traits will lead to the adoption of more and better markers by the cow-calf producers. However, due to the antagonistic relationships between production traits and reproduction (Johnston et al., 2009; Collis et al., 2012), care must be taken to insure that this is not at the expense of reproduction as has happened in the dairy industry. Many growth and development genes influence the development of the female reproductive tract. Therefore, if SNP panels are developed for production traits it will be important to include markers for reproductive performance as well to minimize antagonistic impacts on fertility.

Will We Be Able to Identify Genetic Markers of Fertility?

The first attempt to identify chromosomal regions that influenced reproductive traits in beef cows was the identification of quantitative trait loci influencing ovulation rate in the Twinner cow population at the U.S. Meat Animal Research Center (Kappes et al., 2000). This clearly demonstrated that the low heritability of reproductive traits did not preclude the use of genomic technologies to identity regions of chromosomes that associated with a reproductive trait. As the technology advanced and the high density SNP chips became available for genotyping, a study was performed in Brahman heifers in Australia to identify chromosomal regions associated with age at puberty (Fortes et al., 2010). The results demonstrated the reason for the low heritability of these traits was because there were many significant SNPs each with a very small effect influencing this trait. Similar results were obtained for age at puberty in the Germplasm Evaluation population at the U.S. Meat Animal Research Center (Snelling et al., 2012). This suggests that to provide genetic markers that explain a significant amount of the variation in age at puberty, it is going to take a large number of these markers. This will most likely be true for any reproductive trait. Therefore, to develop a panel that explains a significant portion of variation in reproductive capacity will require a relatively large number of markers.

Pharmacogenetics

Variation in the genetic sequence that results in a change in the function of the encoded protein makes the best genetic markers because their identity and function can be clearly understood. However, the identification of functional polymorphisms within a gene is the most difficult aspect of this work. In human medicine polymorphisms in the follicle stimulating hormone receptor are already being used to predict response to exogenous follicle stimulating hormone (Greb et al., 2005a; Greb et al., 2005b) in an attempt to tailor hormone doses based on the individual genotype. The common hormones used in synchronization of estrus and multiple ovulation embryo transfer (**MOET**) [gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), and prostaglandin F2α (PG)] all work through protein receptors. Therefore, it is easy to envision how functional polymorphisms that change how these receptors interact with a hormone or elicit a cellular response to a hormone could help explain individual animal variation in the response to synchronization of estrus or MOET protocols. For example, a polymorphism in the ionotropic glutamate receptor AMPA1 (GRIA1) has been reported to influence ovulation rate in MOET protocols (Sugimoto et al., 2010). The polymorphism was reported to be functional, because it changed the amino acid sequence. This altered form of the receptor resulted in decreased GnRH secretion. Furthermore, cows carrying this polymorphism were reported to have a decreased luteinizing hormone (LH) surge after synchronization with prostaglandin F2α and decreased conception to artificial insemination. However, in a study at the U.S. Meat Animal Research Center there was no difference in the number of antral follicles between beef cows carrying this polymorphism and cows without the polymorphism (Figure 3). This demonstrates how difficult the identification of functional polymorphisms can be.

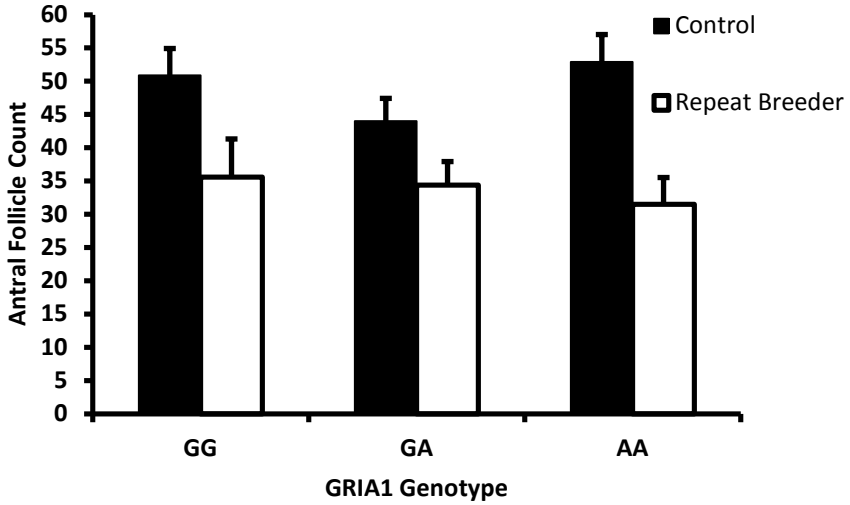

Figure 3. Influence of GRIA1 genotype on antral follicle count in crossbred beef cows differing in fertility. Repeat Breeder cows (n = 64) had fewer follicles than Control cows (n = 72) that had always produced a calf; however, genotype did not affect the number of follicles.

Summary

The reproductive traits with the greatest heritability are those associated with attaining sexual maturity. While it is apparent that these are polygenic traits that will require large numbers of genetic markers to accurately estimate a replacement female's genetic merit, genomic technologies have reached the point where generating genotypes that provide a fair degree of coverage of the genome of cattle is achievable at a cost. The markers that are most likely to be implemented are those that associate with production traits, food safety, and disease resistance. However, the antagonistic genetic correlations between production traits and reproduction suggest the need for the inclusion of genetic markers for reproductive capacity in such panels. As we increase our understanding of the variation in genes that affect how they function, there may be an increased opportunity to harness this knowledge to better control the response of individual animals to exogenous hormones. However, identifying functional polymorphisms and clearly proving that they are indeed functional is very difficult.

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Notes