

Breeding Focus 2021 - Improving Reproduction

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Contents

Preface	iii
Review: Cattle fertility and genetic improvement of fertility in developing countries <i>Eva M. Strucken</i>	5
Reproductive challenges in abalone breeding <i>Natasha A. Botwright, Omar Mendoza-Porras, Roger Chong, Ya Zhang and Carmel McDougall</i>	17
Opportunities from understanding health and welfare of sows <i>Laura Vargovic, Jo Harper and Kim Bunter</i>	37
Saltwater crocodile (<i>Crocodylus porosus</i>) embryo survival: risk factors <i>Sally R. Isberg and Peter C. Thomson</i>	49
New phenotypes for genetic improvement of fertility in dairy cows <i>Irene van den Berg, Melissa Stephen, Phuong N. Ho, Mekonnen Haile-Mariam, Claire Phyn, Susanne Meier, Chris Burke, Nicole Steele and Jennie E. Pryce</i>	59
The influence of bull fertility on beef herd productivity <i>Laercio R Porto-Neto, John Bertram, Marina R S Fortes, Pamela Alexandre, Michael McGowan, Ben Hayes and Antonio Reverter</i>	71
Improving reproductive performance in pigs <i>Jo-Anne Harper, Kim Bunter and Laura Vargovic</i>	85
Breeding for improved fertility of honey bees <i>E.A. Frost, N.C. Chapman, R.G. Banks and S. Hermesch</i>	97
Examining the relative importance of female reproduction in beef breeding herds when fully accounting for production costs <i>Bradley J Walmsley</i>	111
Improving reproduction in ewes <i>Kim Bunter, Andrew Swan and Daniel Brown</i>	127

Selection for reproductive efficiency in turkeys and broiler chickens: egg production, hatchability and fertility	143
<i>Bayode O. Makanjuola, Emhimad A. Abdalla, Christine F. Baes and Benjamin J. Wood</i>	
Genetic improvement of cow reproduction in northern Australia beef cattle breeds	151
<i>Kirsty L. Moore, Matt L. Wolcott and David J. Johnston</i>	
Climatic constraints facing sheep reproduction	163
<i>Gordon Refshauge and Simon de Graaf</i>	
Lamb survival, a challenge for the decades	187
<i>Sabine Schmoelzl, Lynden Smith, Amellia Redfearn and Rachelle Hergenhan</i>	

Preface

“Breeding Focus 2021 – Improving reproduction” is the fourth workshop in the series. The Breeding Focus series was developed to provide an opportunity for exchange between industry and research across a number of agricultural industry sectors. With this goal in mind, workshops have included presentations across multiple agriculturally relevant animal species to take participants outside their area of expertise and encourage them to think outside the box. Reproduction is a main driver for profitability and genetic gain. We will discuss existing knowledge, identify gaps and explore genetic and management strategies to improve reproduction further in multiple species.

Successful reproduction is a complex characteristic comprising the formation of reproductive cells, successful mating and fertilisation, embryonic and fetal growth and eventually a successful birthing event. In livestock species, reproduction traits have mostly low heritabilities, which makes it challenging to improve reproduction as part of a multiple trait breeding objective. The complexity arises not just from the cascade of processes required to result in successful reproduction, but the relevant traits are different in males and females and they are influenced through health and fitness, nutrition, climate and other environmental and management factors.

Challenges to the improvement of reproduction can vary widely for different species. For less domesticated species such as abalone, the ability to produce and reproduce the animals in captivity presents a major challenge. In bees, reproduction has not been given great attention and little research has been undertaken to understand the underlying genetics of drone and queen reproduction. However, in all industries reproduction is recognised as the basis for genetic and economic gain. It directly influences the selection intensity that can be applied. It also determines how many animals are not required for replacement and can be sold. In all industries, irrespective of the challenge, cost-effective and easy to measure phenotypes of reasonable heritability are central. New technologies and approaches enable the development of novel phenotypes for genetic improvement which will be combined with a growing amount of genomic data in livestock species and together these developments provide new and exciting opportunities to improve reproduction further.

We would like to thank everyone who has contributed to this event for their time and effort: the authors for their contributions to the book and presentations, the reviewers who all readily agreed to critique the manuscripts. We would like to express a special thanks to Kathy Dobos for her contributions into the organisation of this workshop and the publication. Thank you!

Susanne Hermesch and Sonja Dominik

Armidale, May 2021

Review: Cattle fertility and genetic improvement of fertility in developing countries

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Abstract

Cattle fertility is generally described as the ability to reproduce. However, fertility is a complex trait and the end result of a living and healthy calf is shaped by many interacting factors including the genetics of both cows and bulls. A multitude of traits have been defined to measure fertility and provide a way to enhance the ability to reproduce through genetic improvement, but most traditional traits are found to be lowly heritable such as calving to first insemination, first to successful insemination, or non-return rate. Nonetheless, including these traits into breeding objectives alongside production traits has improved overall productivity of cattle herds and is now common practice in most developed countries. In developing countries, however, the largest obstacles are reliable recording of phenotypes and the highly variable and often challenging environmental conditions which strongly influence the expression of fertility traits. Breeding for other traits, such as heat tolerance or disease resistance, can however indirectly improve fertility. Studies on *Bos indicus* cattle and other native breeds show that there is phenotypic variability between breeds and that some fertility traits, such as onset of puberty, are highly heritable. Until the infrastructure for phenotypic recording, the expertise for genomic evaluations, and the distribution channels of suitable genetics (artificial or live breeding stock) is established within developing countries, the most promising possibility to increase cattle fertility remains in the improvement of environmental and management conditions. However, enabling developing countries to establish and maintain these infrastructures themselves should be the primary goal to enhance breeding progress.

Biology of Fertility

Fertility defines the ability to reproduce. The more offspring an animal produces during a lifetime, the more fertile this animal is. The possibility of reproduction sets in when an animal reaches puberty which is controlled by an interplay of hormones (Kinder *et al.* 1995; Akers *et al.* 2005; McGowan *et al.* 2018). In brief, puberty in both cows and bulls is initiated when the hypothalamus produces the hormone gonadotropin which stimulates through a cascade of other hormones further development of the ovaries and testes. The ovaries in cows then begin releasing oestrogen and progesterone, whilst the testes in bulls begin producing testosterone.

These hormones orchestrate the onset of oogenesis and spermatogenesis accompanied by physical changes such as general growth, development of the mammary gland in cows and increase in testicular size in bulls (Kinder *et al.* 1995; McGowan *et al.* 2018).

External factors such as nutrition (energy balance) or stressors (heat, transportation, and diseases) around the time of planned conception has been identified to reduce conception success (Buckley *et al.* 2003; Negussie *et al.* 2013; Kenny and Byrne 2018; Negrón-Pérez *et al.* 2019). For the purpose of this article, however, the genetic background of fertility shall be investigated further.

Genetics of Fertility

Cattle fertility is a complex trait enabled by a balanced interaction of many factors. These factors are controlled by many genes or gene variants each with often small effects which makes it difficult to identify genetic loci. Nonetheless, multiple quantitative trait loci and specific genes have been proposed in relation to cattle fertility.

The large availability of controlled data from major cattle breeds from developed countries allowed to identify several genetic loci impacting fertility on a multitude of levels. Selection against identified lethal alleles has largely increased fertility in US Holstein (Taylor *et al.* 2018). Large scale genome-wide association and gene expression studies have identified multiple loci affecting puberty and female fertility in different cattle breeds (Ashwell *et al.* 2004; Guillaume *et al.* 2007; Druet *et al.* 2008; Fortes *et al.* 2016). Chromosome 1 alone was found to include ten potential candidate genes (Cai *et al.* 2019). Amongst the genes that were identified to affect fertility are *FRAS1*, *ITGB5*, *SEMA5B*, and *ADCY5*, the first three are upregulated in the placenta (Fagerberg *et al.* 2014), and the *ADCY5* gene has been associated with low birth and placenta weight, and ovarian morphology (Li *et al.* 2021).

Sperm delivers the sire's DNA and factors that are required for fertilization and embryonic development. The correct development of sperm largely impacts male fertility and begins with the development of the testis and spermatogenesis during puberty. Multiple genes have been identified to regulate this male development and in particular to impact sperm cell energy metabolism, calcium regulation and signalling, and membrane fusion, such as the *FERIL5*, *CNNM4* and *DNAH3* genes (Rezende *et al.* 2018). Often, conception (i.e. the fertilization of the egg) is achieved but a large proportion of embryos fail to develop. Differences in DNA methylation patterns (which genes can be transcribed and which are silenced) impact early embryonic development and fertility (Kropp *et al.* 2017). The same authors showed that 98 genes were differentially expressed between bulls with high or low fertility and that 76 genomic regions were differentially methylated. Most notably, the *TFB2M* gene is an important initiation factor for RNA synthesis in the mitochondria of the cell and was shown in a knockout experiment to decrease the development of blastocysts (Kropp *et al.* 2017; Ramachandran *et al.* 2017).

A few well known genes for fertility, such as the *Leptin* gene, have been tested in indigenous breeds of India (Singh *et al.* 2020; Yadav *et al.* 2020). Selection signature studies specifically in *Bos indicus* breeds have revealed regions or new genes associated with reproductive performance (Maiorano *et al.* 2018; Melo *et al.* 2018), showing that research into cattle fertility should be expanded from exotic *Bos taurus* breeds to more relevant breeds for developing countries.

Breeding for Fertility

Whilst some specific fertility traits such as ovarian development or sperm cell energy metabolism have been associated with particular genes, it has been shown that candidate gene selection for a polygenic trait can be detrimental to overall production due to correlated antagonistic effects. Therefore, breeding indices include multiple traits to allow for a balanced selection (Osteras *et al.* 2007; Boichard and Brochard 2012). The advent of genomic selection allowed to consider the entire genome without requiring the knowledge of exact genetic regulations (Meuwissen *et al.* 2001; Goddard 2009), however, accurate phenotype recording is still necessary and related reference populations essential.

In order to improve a trait through breeding, one must first define a trait and then be able to measure it. Most traits measuring fertility are recorded on cows and even the few traits recorded on bulls, such as semen quantity and quality, are not routinely included in genetic evaluation programs, even in developed countries, although research into genetic parameters of semen attributes is picking up (Butler *et al.* 2020; Butler *et al.* 2021). In some countries, however, breeding values for scrotal circumference are available in beef cattle. A larger scrotum is associated with a higher quality and quantity sperm production and better fertility in daughters (Garmyn *et al.* 2011; Kastelic 2014). Female traits used for genetic improvement cover for example non-return rate (NRh/c) after 56 days of insemination, and number of services per conception (SPC), or interval traits such as the days between calving to first insemination (CFc) and between first to successful insemination (FLh/c), days open (DO, calving to conception), and the calving interval (CI; **Figure 1**). For bulls, a trait measured on their daughters is the daughter pregnancy rate (DPR) which is defined as the percentage of cows actually becoming pregnant within a defined period (often 21 days).

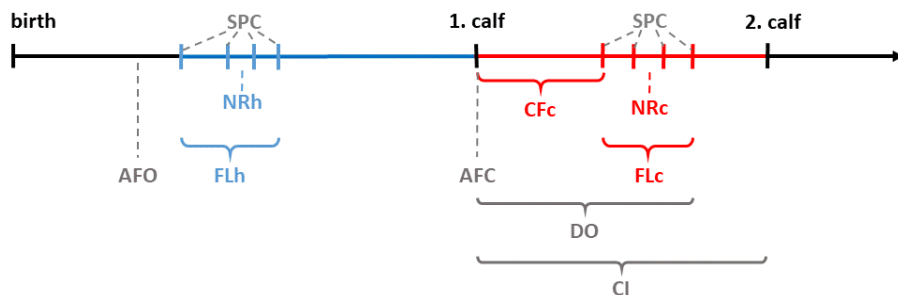


Figure 1. Definition of most common fertility traits measured in cows

AFO: age at first oestrus; AFC: age at first calving; SPC: number of services per conception; NRh/NRc: non-return rate after 56 days of insemination for heifers and cows; CFc: calving to first insemination FLh/FLc: days from first to successful insemination for heifers and cows; DO: days open (CFc + FLc); CI: calving interval

Despite the inclusion of fertility traits into breeding programs, which was done in some developed countries more than 25 years ago (e.g. VIT, Germany), the low heritability of fertility traits has only allowed a slow improvement (Wall *et al.* 2003; VanRaden *et al.* 2004; Fleming *et al.* 2019). With low heritabilities of the traditional fertility traits described above ($h^2=0.01-0.07$) (Liu *et al.* 2008; Liu *et al.* 2017; Häggman *et al.* 2019), new traits are being defined and recorded for selection to improve fertility. Recently, a reproductive tract size and position score system was introduced including ovulation failure, pregnancy per insemination, concentration of pregnancy-associated glycoproteins, and pregnancy loss in lactating cows (Young *et al.* 2017). The size and position of the reproductive tract has been shown to be associated with fertility traits such as ovulation failure, number of pregnancy per insemination, or pregnancy loss based on this scoring system (Madureira *et al.* 2020). Another recent study showed that endocrine fertility traits that measure hormone activity have higher heritabilities, for example commencement of luteal activity ($h^2=0.24-0.32$) or days from calving to first heat ($h^2=0.19-0.33$) indicated by progesterone levels in milk (Häggman *et al.* 2019).

In developing countries, only a limited spectrum of the described fertility traits is recorded. Most animals are kept by smallholder farmers and the ability of the farmer to record the trait and make use of it will determine further uptake of fertility traits.

Cattle Fertility in Developing Countries

Current improvement approaches within developing countries vary by production system and it is not only the development of a breeding program, but the characterization of breeds, the identification of breed compositions, and the large variation in environmental conditions that

are of importance in these countries (Marshall 2014; Kariuki *et al.* 2017; Strucken *et al.* 2017; Marshall *et al.* 2019). The uptake of modern selection such as (genomic) breeding values and breeding methodologies in most developing countries is limited largely by the lack of cheap recording systems that provide reliable and frequent phenotypes (Ducrocq *et al.* 2018). Whilst fertility ranks within the top three important traits for farmers in developing countries (Desta *et al.* 2011; Traoré *et al.* 2017), lack of infrastructure as well as a routine evaluation system is the greatest obstacle for fertility improvement through breeding (Ducrocq *et al.* 2018; Marshall *et al.* 2019).

The import of improved cattle genetics from developed countries has long been practised and is still being promoted by large breeding companies as an easy and fast way to enhance productivity in developing countries. Besides importing live animals to establish new herds, crossbreeding between exotic and local breeds is a favoured practice. Crossbred cattle have the advantage of increasing milk production or body size for draught animals whilst keeping favourable traits from the indigenous breeds, like trypanotolerance (Traoré *et al.* 2017). Trypanosoma are parasites transmitted by tsetse flies and cause poor productivity, higher mortality and lower fertility in cattle (Morrison *et al.* 1981; Bittar *et al.* 2015). However, the effectiveness of this practice has come under scrutiny as it is often futile to select stud animals based on breeding values estimated for an environment that is different to where the production herd is kept. Genomic breeding values for milk yield estimated in Australia or France for stud animals from India (sufficient genomic connectedness was given) for example have a correlation (r) to phenotype breeding values estimated within India of less than 14% (private communication). This demonstrates that the milk yield records of daughters kept in India result in a different ranking of bulls compared to the phenotypic data that primes the genomic breeding values in Australia and France. Considering that most fertility traits are less heritable than production traits makes it even more important to collect phenotypes in the final production environment. Research into genotype by environment (GxE) interactions is on the forefront to understand why and how the same genotypes result in different performance levels when the animal is kept in different environments (Haile-Mariam *et al.* 2008; Zhang *et al.* 2019). To study GxE, however, phenotypes must be recorded on related animals under different environments, i.e. in developing countries.

Environments of developing countries are highly diverse and livestock producers often face unfavourable conditions such as heat, diseases, or poor fodder quality. These conditions affect the accurate recording especially of lowly heritable traits like fertility, which fluctuate stronger in their expression due to environmental influences. As such it is not surprising that many studies in developing countries have investigated fertility in relation to environmental factors. Scrotal damage caused by ticks has been shown to reduce the fertility of communal bulls in South Africa (McCrindle *et al.* 2019). Begait cattle from Ethiopia had shorter calving intervals and were younger at first calving if kept in a better environment (Mezgebe *et al.* 2018), and cows from smallholder farms in Vietnam had longer waiting periods if they calved in the rainy season (Nguyen-Kien *et al.* 2017).

Breed differences regarding fertility between native cattle or imported exotic cattle have also been reported. Samkange *et al.* (2019) showed that the Nguni breed had better conception rates and significantly shorter calving intervals in the semi-arid conditions of Namibia compared to Afrikaner or Simmental cattle. Ankole cattle from Rwanda showed lower fertility on a number of measured traits including calving interval compared to crossbreeds (Manzi *et al.* 2019). Imported Brown Swiss cattle showed a higher reproductive efficiency, pregnancy rate, and shorter calving intervals in Egypt compared to Holstein cattle (El-Tarabany and Nasr 2015). These breed differences show that there is room for improvement of either breeding exotic cattle in different environmental conditions, or improving native cattle breeds.

Bos indicus cattle, which are largely distributed across developing countries due to their adaptation to heat and local diseases, have a late onset of puberty and longer calving intervals compared to *Bos taurus* cattle (Abeygunawardena and Dematawewa 2004). However, age at puberty has been shown to be highly heritable with h^2 between 0.2-0.67 (Abeygunawardena and Dematawewa 2004; Nogueira 2004), which opens up the opportunity to change this trait through selective breeding.

Other traits not directly related to fertility can also play an important role in improving fertility in developing countries. For example, it is known that inbreeding has a negative effect on fertility traits, also known as *inbreeding depression*. Moreover, it has been shown that it is particularly recent inbreeding that has unfavourable effects on fertility, whilst ancient inbreeding was even associated with favourable effects on fertility (Makanjuola *et al.* 2020). Heat and disease stress impacting fertility are challenges faced by most cattle breeders in the developing world, however, improved resilience to heat and diseases can be achieved through breeding (Bohmanova *et al.* 2008). Cows that tolerated heat better were shown to conceive faster (Nanas *et al.* 2020), and even epigenetic effects that impact the fertility of the next generation have been suggested (Huber *et al.* 2020). A single nucleotide polymorphism in the *ATPIA1* gene was associated with rectal temperature and heat tolerance (Kashyap *et al.* 2015), and Australia has recently introduced a breeding value for heat tolerance (Nguyen *et al.* 2017), which could be of interest to tropical developing countries.

The largest improvement of fertility in both developed and developing countries, however, was made through the introduction of artificial insemination (AI) (Rodriguez-Martinez 2012). However, many *Bos indicus* cattle have a short and hard to detect oestrus and their temperament negatively impact the application of AI (Bó *et al.* 2007). Fixed-time AI with oestrus synchronization through administration of hormones has been tested on *Bos indicus* cattle and are promising (Rekwot *et al.* 1999; Bayemi *et al.* 2015). Artificial insemination (AI) is the most widely applied biotechnology and many developing countries wish to extend its use, however, the lack of infrastructure is still often an obstacle (Yitayih *et al.* 2017). Another technology that could improve fertility is the use of embryo transfer to circumvent infertility due to heat stress causing changes to ovarian function and reduces oestrus detection (Baruselli *et al.* 2020). However, due to high costs and lack of technology, adoption rates in developing countries are minimal (Mebratu *et al.* 2020).

Until the infrastructure for reliable phenotype recording and the expertise to evaluate the collected information is established, the best way to enhance fertility within developing countries remains through improvement of environmental and management conditions. Research into GxE, to allow a better prediction about how imported exotic genetics might or might not be beneficial in a developing country, is important, but enabling a countries' self-sufficient recording and evaluation system should be the primary goal. Once the infrastructure is established, faster and more targeted genetic improvement will become possible within developing countries.

Summary

1. Characterization of indigenous breeds and identification of breed compositions are important in developing countries to match the best breed types to existing environments (Marshall 2014)
2. The accurate recording of phenotypes within the production environments of developing countries needs to be strengthened. Developing countries often face unfavourable environmental conditions which complicate the accurate recording of lowly heritable traits such as most traditional fertility traits (Ducrocq *et al.* 2018).
3. The expertise for data processing, evaluation, and application needs to be increased within developing countries (Ducrocq *et al.* 2018; Marshall *et al.* 2019).
4. Infrastructure needs to be strengthened, for example for the distribution of biotechnologies and the collection of accurate trait records needs to be strengthened (Yitayih *et al.* 2017; Ducrocq *et al.* 2018; Mebratu *et al.* 2020).

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