

Review article

Reproduction and genetic improvement in dairy cattle: Sustaining a critical link in the era of opportunities

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HIGHLIGHTS

- Genomic selection and reproductive biotechnologies have reversed historical declines in fertility, yet fertility remains underemphasized in most breeding objectives.
- Emerging tools—including novel phenotypes, functional genomics, male-fertility evaluations and genome editing—expand the scope for sustainable genetic improvement of fertility.
- The review highlights the delicate balance among genetic gain, biological constraints and management practices, stressing the need for continuous monitoring to ensure long-term sustainability.

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ABSTRACT

Fertility and genetic improvement are fundamentally interdependent in dairy cattle breeding: reproductive success determines the realization of genetic gain, while selection decisions shape the genetic capacity for reproduction. Historically, fertility declined because breeding objectives prioritised milk production, trait definitions captured only a narrow portion of reproductive biology, heritability was suppressed by strong environmental influences, and phenotypic data were often incomplete or imprecise, a limitation that still affects fertility evaluations in many systems. Although genomic selection has reversed long-standing negative trends and enabled more balanced breeding goals, fertility traits still receive comparatively low emphasis in selection indices. This underrepresentation is further sustained by extensive reliance on management interventions—particularly hormonal synchronisation—that improve phenotypic fertility in the short term but risk obscuring genetic variation, biasing evaluations and conflicting with societal expectations for sustainable livestock systems. This review synthesises fertility within three complementary domains: the biological mechanisms underlying reproduction, the genetic architecture and evaluation systems used to improve it, and the management practices that shape the phenotypes on which selection depends. Across these domains, recent progress has been considerable. Genomic selection has increased the accuracy of breeding values for low-heritability traits, reproductive biotechnologies have intensified selection and shortened generation intervals, and emerging indicator traits, high-throughput phenotyping and richer genomic resources offer new opportunities to align fertility evaluations more closely with underlying biology. Developing evaluations for male fertility, meanwhile, represents an accessible additional avenue for strengthening genetic improvement. Looking ahead, genome editing and advanced reproductive interventions offer unprecedented potential to overcome genetic constraints, yet their practical use remains limited by current evaluation methodologies, the need for robust and biologically meaningful fertility phenotypes and societal acceptance of biotechnological innovation. Taken together, the evidence underscores that progress in fertility will depend not on individual technologies alone, but on maintaining alignment across the biological, genetic and management domains. Only when these dimensions operate synergistically—supported by coordinated strategies among key stakeholders including breeding organisations,

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AI companies, producers and laboratories—can selection act effectively on fertility, ensuring long-term reproductive resilience and the sustainability of dairy cattle breeding.

The role and biological determinants of fertility

Fertility is a complex process involving several critical stages. After calving, cows undergo uterine involution, followed by the resumption of estrous cycles and the manifestation of heat signs. Observing these signs is basically essential for timely insemination and successful fertilization of the ovulated oocyte – ovulation occurs 15–22 h after the end of heat (De Rensis et al., 2024). Fertilization, which takes place in the oviduct, results in the formation of a zygote, however it does not guarantee reproductive success. The zygote must develop into an embryo, grow and migrate to the uterus to attach to the endometrial lining in a process known as implantation – on that time the pregnancy can be recognized (Ortega et al., 2018). Thus, achieving reproductive success requires not only embryo formation but also successful implantation and the maintenance of pregnancy (Lucy, 2019).

Successful conception and maintenance of pregnancy are fundamental definitions of fertility in dairy cattle. From the farmer's perspective, calving is sometimes also regarded as a fertility trait but in this analysis, it is not regarded as such. Higher fertility reduces inseminations per conception, shortens calving intervals and age at first calving, and thereby improves reproductive efficiency and productivity.

Milk production, the cornerstone of both dairy farming and breeding, is fundamentally dependent on the reproductive success of females. Following successful insemination of a heifer or cow, pregnancy begins, culminating in calving, which initiates lactation and results in the birth of a calf. Efficient reproduction is fundamental to breeding, which relies on selecting genetically superior animals and using them to create the next generation. The more effectively reproduction is carried out, particularly in the animals with the highest genetic merit, the greater the genetic progress due to enhanced selection intensity, partly because improved fertility reduces involuntary culling. Rapid and efficient reproduction in animals at a young age contributes to shortening the

generation interval—another key driver of genetic progress. Furthermore, when reproductive biotechnologies enable wide access to genetically superior animals, they facilitate the rapid dissemination of genetic progress, thereby enhancing improvement across the entire population.

Fertility issues in female dairy cattle not only impede genetic improvement but also contribute significantly to economic losses. According to recent studies (Agriculture, 2022), these problems are among the most prevalent causes of culling. A delayed age at first calving in heifers extends the time required to recoup the investments made in raising the heifer and reducing the profit derived from her milk production. The economic losses associated with reproductive disorders are difficult to quantify, particularly since the occurrence of one disorder often predisposes cows to others (Wicaksono et al., 2025). Costs arise mainly from reduced milk yield, culling, veterinary services, and treatments, while feed, calving, and labor contributed comparatively little. This study, based on Dutch data, estimated the mean annual cost of reproductive disorders at approximately €100 per cow when dystocia, retained placenta, metritis, endometritis, anovulation, cystic ovarian disease, and sub-estrus were jointly considered.

Because fertility arises from the interaction of biological processes, genetic variation and herd-level management, its improvement requires an integrated perspective. Throughout this review, we consider fertility within three analytical domains: the biological mechanisms underlying reproductive success, the genetic architecture influencing these mechanisms and the management practices that shape the phenotypes used in breeding programs. Recognizing how these domains interact is essential for interpreting historical trends in fertility and for identifying opportunities for sustainable genetic progress. To facilitate navigation through the complexity of fertility improvement, Fig. 1 provides a simplified conceptual overview of the main domains discussed in this review and their interconnections. The figure serves as a guide for the subsequent sections, which elaborate on each component in greater detail.

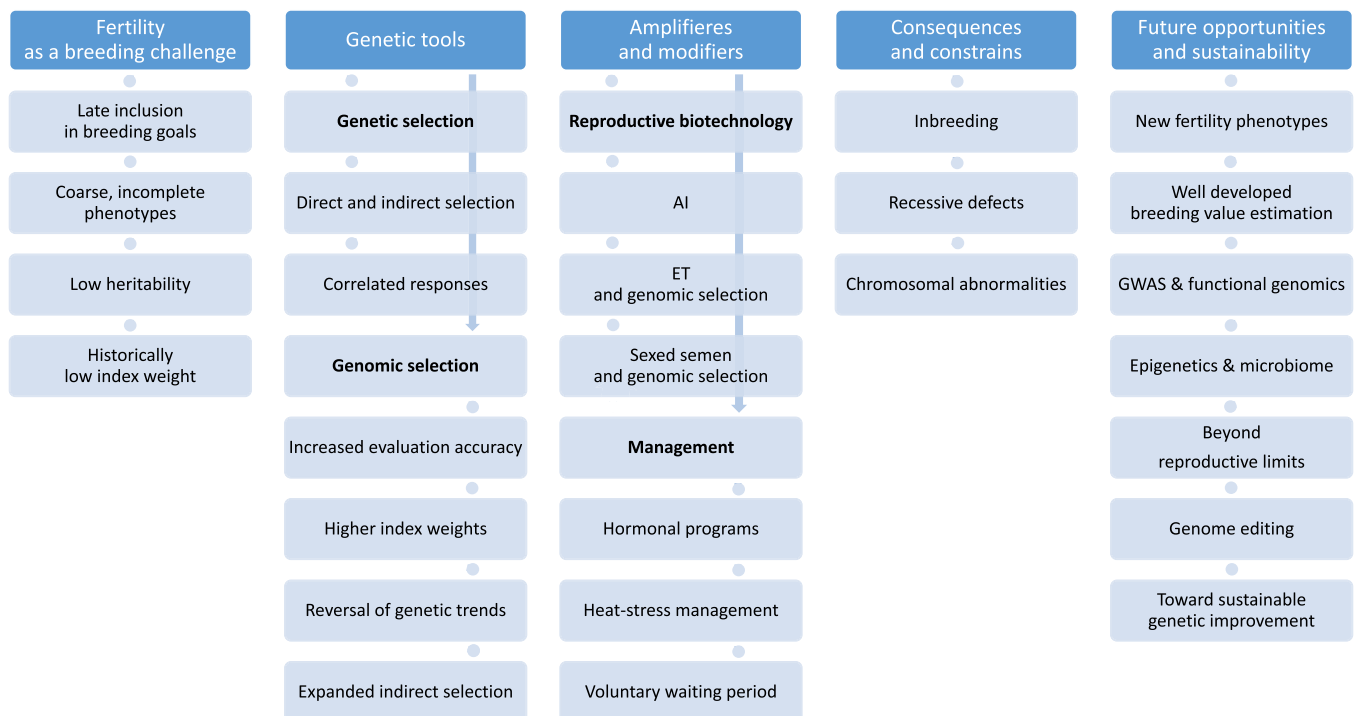


Fig. 1. Conceptual framework guiding fertility improvement in dairy cattle breeding.

Genetic selection for fertility

The complex nature of fertility involves numerous environmental influences and many genetic components controlling successive reproductive processes. Environmental factors such as herd management and nutrition—which vary across years, seasons, and even months—as well as age at calving and age at insemination within parity, have been shown to significantly affect fertility traits (Hayes et al., 1992; Thaller, 1998) and are routinely accounted for in genetic evaluations. Non-genetic influences also include management decisions such as hormonal interventions and voluntary waiting period (VWP) policies, which are discussed in more detail later in this paper. Beyond on-farm management, additional variation arises from semen dilution procedures, the sire's age at collection, and the AI technician's skill. Although genetic differences in sire fertility exist, they are often overshadowed by environmental effects, particularly those related to semen storage and handling before insemination.

Reproductive success is controlled by paternal, maternal, and embryonic factors (Diskin and Morris, 2008; Kropp et al., 2014). From a genetic improvement perspective, many of these factors are genetically determined and can be effectively improved in breeding programs. Although fertility traits, as polygenic, are heritable and exhibit high overall genetic variance, they contain a relatively low proportion of additive genetic variance and a substantial contribution of non-additive components. Natural selection reduces genetic variation because alleles that lower inclusive fitness decline in frequency, and—as shown in the unified Fisher's fundamental theorem of natural selection—inclusive-fitness framework (Bijma, 2010)—their loss occurs at a rate proportional to the additive genetic variance in fitness. Initially, however, the unfavourable genetic correlations between fertility and production traits were of greater concern than the heritability of fertility itself. For many years, genetic improvement in cattle was successfully but unilaterally focused on production traits.

Several factors make the genetic improvement of fertility particularly challenging. The biological complexity of fertility means that no single trait can capture it comprehensively, and the indicators currently in use may fluctuate widely in small herds due to random environmental effects. Heritability estimates for key fertility traits remain low—for example, in American Holsteins, heritabilities for primary fertility traits are only 1–4 % (VanRaden et al., 2004). Low heritability and limited additive genetic variance are not the only constraints, as fertility traits integrate multiple underlying biological processes whose genetic architecture remains incompletely characterized. A further fundamental difficulty is that traits that are easy or inexpensive to measure on a large scale are not always well aligned with the underlying biology of reproduction.

Effective selection requires accurate evaluations, which depend on both the quantity and quality of available data. Historically, birth and calving dates were often the only information used to evaluate fertility traits. Later insemination dates were incorporated, yet even today many populations struggle to collect complete insemination records. The accuracy of breeding value estimation for fertility traits can be improved by incorporating additional information, such as indicators of sexed-semen use (Tyrisevä, 2017) or explicit confirmation of conception dates (Bowley et al., 2015). The increasing adoption of electronic record-keeping systems (Hermans et al., 2017) has expanded data volume, but not always data quality: for example, on farms that stock both conventional and sexed semen from the same bull, matings may be misclassified between these categories. In such cases, more records do not necessarily translate into better information.

The limited scope and incomplete nature of fertility-related data reduce the reliability of breeding value estimation and thus constrain the effectiveness of selection aimed at improving fertility. In some fertility evaluations, nearly half of the herds may show no within-herd variability for certain traits (Strabel, 2025), which further undermines their usefulness. By contrast, some countries achieve high data completeness:

in Denmark, pregnancy is confirmed for essentially all cows and health status is recorded for about 90 % of animals (Borchersen, 2017 - personal communication). In populations without systematic pregnancy confirmation, the date of successful insemination is often inferred from gestation length, which reduces accuracy and delays data availability, as reliable information is obtained only if the cow remains in the herd and survives to calving.

Direct selection

Although both sexes contribute to reproductive success, genetic improvement of fertility has primarily focused on traits measured in females. Because direct physiological measurements are impractical at scale, fertility traits are defined using event records—calving dates, insemination dates, and optional pregnancy diagnoses—which, despite their simplicity, capture the essential biological components of the reproductive cycle. In the following sections, we use predominantly U.S. trait definitions and evaluation practices as illustrative examples, while acknowledging that alternative definitions exist in other breeding populations. These traits align naturally with the five trait-group categories established by Interbull, which cluster common definitions used internationally. An overview of how these traits are constructed from event dates and assigned to the Interbull categories is provided in Fig. 2. Despite the existence of standardized categories, substantial international variation in trait definitions persists. As Sendecká (2022) documented, 22 participating Interbull populations collectively record 16 different fertility traits, often with overlapping definitions that yield high genetic correlations. Even the most commonly reported trait—calving-to-first-insemination—is submitted by only 16 countries, while cow conception rate (CCR) appears in just 10. These inconsistencies reduce trait harmonization across populations and complicate international comparison of breeding values.

Calving to conception (interval)

A fundamental measure of fertility is the calving-to-conception interval, also known as days open (DO), which belongs to the Interbull fifth category (Fig. 2). It reflects the time from calving to successful conception and integrates multiple biological steps, including uterine recovery, resumption of cyclicity, expression and detection of estrus, fertilization, and early embryo survival (Lucy, 2019). Because this trait does not require insemination data, it was historically among the first fertility traits included in breeding programs. In U.S. Holsteins, a transformed version of this measure—daughter pregnancy rate (DPR)—is incorporated into the economic index. For genetic evaluation, days-open records are linearly converted to a 21-day pregnancy rate using the formula: pregnancy rate = $0.25 \times (233 - \text{DO})$, and DPR expresses the expected percentage of nonpregnant cows that conceive within each 21-day interval (VanRaden et al., 2004). Thus, higher DPR values indicate that a bull's daughters are more likely to become pregnant sooner, corresponding to roughly four fewer DO per unit of DPR.

Conception rate (heifer conception rate and cow conception rate)

Conception rate quantifies the probability of establishing pregnancy from a single insemination with a fertile mate (Taylor et al., 2018). Separate traits are evaluated for maiden heifers (Heifer conception rate - HCR) and lactating cows (CCR), reflecting their distinct physiology and management and corresponding to the Interbull first and third categories, respectively (Fig. 2). These traits rely on insemination records, making them sensitive to data completeness, recording errors, and the use of sexed semen. A related indicator, the 56-day non-return rate, expresses the proportion of females not returning to estrus following insemination and is used in several countries as a practical alternative to conception rate.

Service period length (cow conception interval)

Traits derived from insemination dates also include intervals

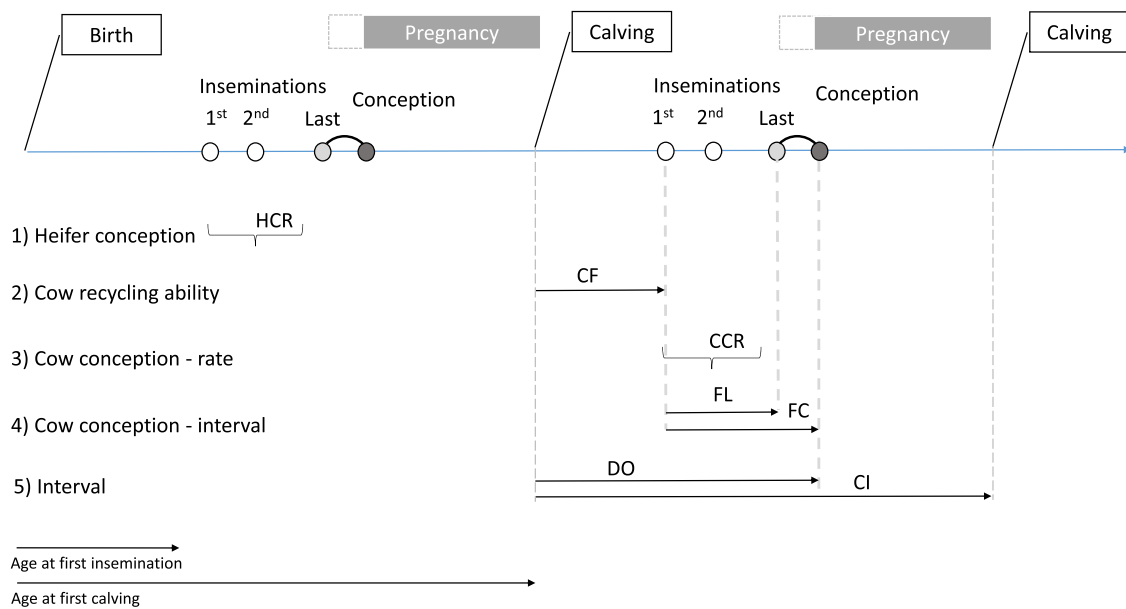


Fig. 2. Basic female fertility traits definition overview with five categories defined by Interbull: “Heifer conception” – which is to measure maiden heifer’s ability to conceive, “cow recycling ability” – lactating cows’ ability to recycle after calving, “cow conception – rate” – lactating cow’s ability to conceive, “cow conception – interval” – as cow conception rate but measured as an interval trait and “interval” – lactating cows’ measurement of interval calving to conception. For each category the recommended trait is presented: HCR and CCR are conception rates for heifer and cow, respectively, CF – a period from calving to the first insemination, FL – a period from the first to the last insemination, FC – a period from the first insemination to conception, DO – days open measured as a period between calving and conception, IC – calving interval measured as a period between consecutive calvings.

representing the length of the breeding period—for example, from first to last insemination or from first insemination to conception, which are grouped in the Interbull fourth category (Fig. 2). The usefulness of these traits depends heavily on the completeness and accuracy of insemination and pregnancy confirmation data. In populations with inconsistent recording, such as the United States (Cole et al., 2024), estimation of breeding values for these traits becomes unreliable. Nonetheless, when high-quality data are available, these measures provide valuable insight into both biological fertility and breeding management.

Return to cycle (cow recycling ability)

The interval from calving to first insemination is widely used to evaluate a cow’s ability to resume cyclicity. Ovulation within the first month postpartum is desirable (Galvão et al., 2010), yet expression of the trait reflects both true biological recovery and management decisions—particularly estrus detection efficiency and farm reproductive strategy. Importantly, this measure is also affected by the VWP chosen by the herd, which can partly mask underlying biological variation. As insemination dates are widely recorded, most countries contributing to Interbull evaluations report this trait in the second category illustrated in Fig. 2.

Age at first calving

Age at first calving reflects heifer development, reproductive maturity, and fertility. In the United States, a reversed-scale version (“early first calving”) was incorporated into the economic index in 2021 due to its favourable genetic correlations with other fertility traits such as HCR, CCR, and DPR (Hutchison et al., 2017). Under this reversed scale, younger calving ages receive higher scores—for example, a heifer calving at 22 months ranks more favourably than one calving at 26 months. A closely related alternative is age at first insemination, which captures similar biological processes but is subject to the same limitations, as both traits are strongly influenced by management decisions regarding the targeted age at first breeding.

Distinguishing heifer and cow fertility

Initially, separating fertility traits for heifers and cows was

questioned, but numerous studies have confirmed that these should be evaluated independently. Genetic correlations between heifer and cow fertility traits often fall below 0.90 (Jamrozik et al., 2005), indicating partially distinct genetic control. Some traits, such as gestation length or calving ease, show strong correlations across parities, whereas others—body condition score (BCS), cystic ovarian disease, lameness lesions, or specific udder traits—appear genetically independent (Oliveira Junior et al., 2021b). Heifer puberty and conception traits have also been proposed as early predictors of later cow fertility (Meier et al., 2021).

Male fertility

Male fertility contributes uniquely to reproductive success through the bull’s role in fertilization, embryo development, and establishment of pregnancy (Immler, 2018; Ortega et al., 2018). In genetic evaluations, sire fertility is typically quantified using sire conception rate (SCR), often adjusted for factors such as sire age and inbreeding level. These data are widely used by AI organizations to manage semen-use strategies and minimize variability among sires (DeJarnette et al., 2008). Bulls also contribute genetically to traits such as stillbirth rate, which affects both conception success and perinatal survival.

Indirect selection

Fertility, being a complex trait that demands substantial physiological resources, is among the first functions to be suppressed when animals face disease or adverse environmental stressors. For this reason, selection that reduces the impact of such stressors—either by increasing resilience, improving the cow’s metabolic efficiency, or lowering disease incidence—represents an indirect genetic pathway to improved fertility.

Fertility is highly sensitive to metabolic stress, disease, and physiological imbalance. Consequently, improving traits that enhance resilience provides an indirect yet effective pathway to genetic gains in reproduction. Longevity—one of the most widely used fitness traits in dairy breeding—captures many of these effects. Because poor reproductive performance is a leading cause of involuntary culling, improving longevity helps sustain fertility indirectly. In U.S. Holsteins, the genetic

correlation between CI and longevity is moderately strong (0.59), supporting their biological connectedness (VanRaden et al., 2004).

Health traits also contribute significantly to fertility. Diseases occurring around the breeding period, particularly mastitis, metritis, ketosis and lameness, have repeatedly been shown to reduce conception rate and lengthen the interval to conception (Daros et al., 2022; Fuenzalida et al., 2015). For instance, the genetic correlation between resistance to mastitis and fertility is favourable 0.20 (Cole and VanRaden, 2018). Given the widespread nature of mastitis—with reports indicating that nearly 40 % of cows in routinely monitored dairy populations show elevated somatic cell counts—improvements in udder health have clear downstream reproductive benefits (PFHbIPM, 2023). In the United States, bulk-tank monitoring shows that 8.9 % of all milk shipments exceed 400,000 cells/mL, indicating that udder-health issues are also far from rare, even though the metric reflects herds rather than individual cows (NAHMS, 2018).

Body condition score and the underlying nutritional physiology provide another indirect selection route. The trait is moderately heritable and genetically associated with several fertility outcomes. As consistently reported, both excessively high and low BCS are linked to reduced ovulation rates, lower first-service conception, increased embryonic loss, and a higher incidence of disorders such as metritis, retained placenta, cystic ovarian disease, and displaced abomasum (Bewley and Schutz, 2008; Lucy, 2001; Rodney et al., 2018). Selection for optimal BCS therefore contributes to improved fertility, as demonstrated in breeding programs such as those in New Zealand (Roche et al., 2009). Recent results further indicate advantageous associations between breeding values for lower body weight and higher reproductive success (Lauber and Fricke, 2023). Importantly, although BCS measured alongside linear type traits is subject to moderate scorer-related variability, it can be reliably predicted from these traits, eliminating the need for additional data collection (Berry et al., 2021).

Calving disorders also play a central role. Dystocia, retained placenta, and uterine infections compromise postpartum recovery and delay the return to ovarian cyclicity (Beagley et al., 2010; Wagener et al., 2017). Therefore, selection for calving ease—historically one of the earliest indirect routes to improve fertility—remains a cornerstone of many national breeding programs (Mangurkar et al., 1984). Together, these indirect pathways reflect biological mechanisms through which improved robustness enhances reproductive efficiency, complementing direct fertility traits in contemporary selection indices; however, this remains an evolving area, and additional emerging indicators are discussed later in the manuscript.

Correlated decline

For decades, dairy cattle breeding programs prioritized production traits, leading to sustained productivity gains but, simultaneously, to unintended deterioration of fertility. From the 1960s to the early 2000s, the strong unfavourable genetic correlations between milk yield and reproductive performance translated into increasingly longer CI, more inseminations per conception, and declining conception rates (Hansen et al., 1983; Hayes et al., 2009; Royal et al., 2002). Fricke and Wiltbank (2022) showed that in U.S. Holsteins the CI increased from 1955 to 2000; notably, much of the improvement observed between 2000 and 2010 resulted from better management—including hormonal programs and increasing energy intake during critical reproductive periods.

Repeat breeding syndrome exemplifies the multifactorial nature of declining fertility. The syndrome is defined as failure to conceive after three or more timely inseminations despite the absence of clinical abnormalities (Gustafsson and Emanuelson, 2002). It has been linked to shortened intervals from calving to first service, increased incidence of mastitis, and greater veterinary treatment rates, underscoring the interconnectedness of metabolic, health, and reproductive processes.

The underlying antagonism between production and fertility arises from both pleiotropy and linkage disequilibrium between loci affecting

milk synthesis, metabolism, and reproductive physiology. Although these mechanisms create real biological opposition, they do not constitute an immutable constraint: recombination gradually breaks down linkage, and pleiotropic pathways can be counterbalanced through multi-trait selection. Importantly, as emphasized by Berry et al. (2016), the inverse association between high milk yield, greater energy demands, and reduced fertility does not imply a simple causal chain. Experimental supplementation aimed at alleviating energy deficits has shown only limited ability to restore fertility, indicating that the decline in reproduction cannot be addressed by nutritional management alone.

A central reason for the historical genetic decline is the late inclusion of fertility traits in total merit indices. Until the mid-1990s, few total merit indices used in dairy breeding programs included traits other than fat and protein yield (Cole and VanRaden, 2018), and most national indices focused almost exclusively on production. In the U.S. Net Merit index, DPR was not introduced until 2003, and it was only eleven years later that additional fertility traits—HCR and CCR—were incorporated (Cole and VanRaden, 2018). By contrast, the Nordic countries were pioneers, including fertility, calving, and health traits as early as 1972; moreover, until 1994, they were the only countries to incorporate these categories into their total merit indices (Heringsstad and Wethal, 2023). When fertility traits began to be broadly adopted into selection indices across Europe, North America, New Zealand, and Australia in the 2000s, the long-standing negative trends in female fertility began to reverse (Carvalho et al., 2018; Miglior et al., 2017).

Today's balanced breeding goals—supported by GS and reproductive technologies—indicate that the antagonism between production and fertility can be effectively mitigated. Many modern programs incorporate numerous fertility-related traits, as well as traits genetically correlated with reproduction, thereby addressing most of the biological steps that underpin successful fertility (Lucy, 2019). Yet the historical lag serves as a reminder that long-term sustainability in dairy breeding requires continuous integration of fertility into core selection objectives.

Genomic selection: pros and cons in fertility

Genomic selection for fertility

Genomic selection (GS) fundamentally reshaped dairy cattle breeding by increasing the accuracy of genetic evaluation and substantially shortening the generation interval, thereby accelerating overall genetic progress and, strengthening selection for low-heritability traits such as fertility. Although the introduction of GS initially reduced the accuracy of breeding values for young bulls, this effect was outweighed by higher evaluation accuracy in females and the much shorter generation interval (Garcia-Ruiz et al., 2016; Guinan et al., 2023).

Although GS initially reduced the accuracy of young bulls, it substantially increased the accuracy of breeding values for genotyped females—most notably improving the relative accuracy of fertility traits, which had previously been much lower than that of production. This improvement removed a key constraint of the pre-genomic era, when the limited reliability of fertility evaluations—compared with the consistently high accuracy of production traits—contributed to their low weighting in total merit indices and, consequently, to unfavourable genetic trends. Because production and fertility are antagonistically correlated, maintaining adequate emphasis on fertility traits is necessary to prevent deterioration of reproductive performance (Berry et al., 2014). The higher accuracy enabled by GS made such emphasis both more feasible and more effective.

As documented by Bouquet and Juga (2013) and Thomasen et al. (2016), the improved reliability of fertility evaluations contributed directly to the increasing weight assigned to fertility traits after 2009, marking a turning point in reversing decades of unfavourable genetic trends. The impact is clearly illustrated in Canada, where fertility traits carried only 5 % weight before 2015 and where favourable genetic trends emerged only after both the adoption of GS and an increase in

emphasis to 13.3 %; these developments coincided with substantial gains in evaluation accuracy (Van Doormaal et al., 2025). A similar pattern occurred in the United States: despite only a modest rise in the weight of DPR in Net Merit (from 9 % to 11 % in 2010), the genetic trend for fertility improved by ~150 % following the introduction of GS (Guinan et al., 2023). More broadly, recent analyses of changes in selection indices indicate that the incorporation of fertility and other functional traits has been accompanied by a shift from unfavourable to favourable genetic trends for fertility, highlighting the combined importance of balanced breeding objectives and improved evaluation accuracy (Cole, 2025). Several other Holstein breeding programs also increased their emphasis on fertility—most notably France, where its weighting more than doubled (from 12.5 % to 22 %) (Mourocq, 2013). Across EuroGenomics member countries (Germany, France, the Netherlands, Denmark, Sweden, Finland, Spain, and Poland), the current emphasis on direct fertility traits averages ~13–14 %, with national values ranging from 7 % to 20 % (Eurogenomics, 2025). These figures, however, represent only direct fertility traits; the effective selective pressure on reproductive performance varies by country and depends largely on the quantity and quality of fertility data available and on the contribution of correlated traits included in total merit indices (see Fig. 2).

Genomic selection also enabled the inclusion of new health and robustness traits closely linked to reproductive success. Disorders such as displaced abomasum, ketosis, mastitis, lameness, cystic ovarian disease, and metritis—previously characterized by low heritability and limited, inconsistent phenotyping—became accessible for routine evaluation when supported by genomic prediction (Zwald et al., 2004). Several of these traits exhibit meaningful genetic associations with fertility; for example, a positive genetic correlation of approximately 0.32 between ketosis and metritis (Koeck et al., 2012), and a correlation of 0.25 between metritis and DO (Neuenschwander et al., 2012). Building on this rationale, Canada incorporated these traits into its Metabolic Disease Resistance Index for Holstein, Jersey, and Ayrshire populations (Jamrozik et al., 2016), and since 2018, CDCB has routinely published six direct health traits for U.S. Holsteins—milk fever, displaced abomasum, ketosis, mastitis, metritis, and retained placenta—many of which contribute, directly or indirectly, to improved fertility.

Beyond health traits, GS has facilitated the development of new indicators grounded in physiological or behavioural monitoring. In Australia, systematic veterinary diagnoses of mastitis, reproductive disorders, metabolic diseases, and lameness have been integrated into GS-based evaluations (Abdelsayed et al., 2017). In several countries, such as Denmark, clinical mastitis diagnoses—often available only from a limited subset of herds—have nonetheless been incorporated into genetic evaluations, providing better results than selection using SCC alone. Additionally, technological advances in herd monitoring generate continuous streams of data on activity, rumination, oestrus expression, uterine health, and metabolic function—offering further opportunities to refine fertility trait definitions and improve the accuracy of their genetic evaluation. Such traits, once measured only in elite or experimental herds, are increasingly being incorporated into research-grade and, in some cases, routine genetic evaluations.

Finally, the synergy between GS and reproductive biotechnologies—particularly embryo transfer (ET), oocyte pickup, and genotyping of embryos—has expanded the capacity of breeding programs to identify and utilize individuals with the highest breeding values at an early age. Similarly, hoof health traits linked to lameness—traditionally recorded only in a minority of herds—have been incorporated into routine evaluations in countries such as Netherlands, the Nordic system, Spain, Poland and Canada. This interplay enables more intensive selection on fertility and related traits, while also shortening the generation interval and amplifying the dissemination of genetic progress across populations.

Genomic selection elevated fertility from a historically low-priority

trait—constrained by limited phenotyping, low heritability and unfavourable correlations with production—to one that can now contribute meaningfully to breeding progress. By increasing the accuracy of female evaluations and supporting the inclusion of additional fertility-related indicators, GS has strengthened the genetic improvement of reproductive performance and enhanced the sustainability of breeding programs. This includes traits such as clinical mastitis and lameness, for which available phenotypes often come from only a limited number of herds. Nevertheless, because production traits continue to carry very high economic weight, their genetic trends remain strongly positive, whereas fertility—although clearly improving—continues largely to recover the deficits accumulated during earlier decades when it received minimal emphasis in selection programs.

Impact of inbreeding on fertility

An adverse consequence of intensive genetic improvement—largely driven by efficient reproduction—is a faster rise in homozygosity. The rate of inbreeding has increased following the implementation of GS, regardless of whether estimates are pedigree- or genome-based (Cole, 2024). That negatively impacts animal performance—a phenomenon referred to as inbreeding depression, which includes the decline of polygenic traits, such as fertility and traits influencing it (Cole, 2024; Parland et al., 2007).

Recent genomic-based indicators further confirm the negative impact of inbreeding on fertility, with a reported increase by 0.34 days in DO per 1 % (Mugambe et al., 2024). The detrimental effects of inbreeding may vary across traits, with reproductive traits being more affected (Antonios et al., 2021; Doekes et al., 2019; Ma et al., 2019). Elevated levels of inbreeding have been also consistently associated with reduced male fertility in dairy cattle (Nani and Peñaricano, 2020; Pacheco et al., 2023). Analyses based on runs of homozygosity (ROH) further support this relationship; Rossoni et al. (2023) identified four genomic regions—on chromosomes 6, 10, 11, and 24—that appeared more frequently in bulls with poor fertility, suggesting these ROH segments may harbor deleterious alleles affecting reproductive performance.

Although selection gains usually surpass inbreeding depression, this is not the case in U.S. Holsteins, where declines in traits such as DPR are not offset by selection (Cole et al., 2024). This highlights the need to balance selection intensity with inbreeding management. Various strategies exist to maintain this balance, including adjusting breeding values for expected future inbreeding (VanRaden, 2005). At the population level, this requires coordinated action among AI organizations (Lozada-Soto et al., 2024). At the herd level, targeted mating strategies can successfully limit inbreeding; for example, Pryce et al. (2012) proposed penalizing matings predicted to produce highly inbred offspring.

Intensive use of reproductive technologies enhances genetic gain but compromises genetic diversity. Reducing generation intervals via ovum pick-up followed by in vitro fertilization significantly accelerates inbreeding per year and per generation, posing a risk to genetic variability (Doublet et al., 2020). Simulation studies show that sustaining diversity requires using more sires and moderate use of reproductive technologies, or alternatively increasing the number of female donors when these technologies are applied intensively (Doublet et al., 2020). When GS is used to control inbreeding not only use of multiple ovulation and embryo transfer (MOET) has to be optimized but also the number of genotyped females (Bouquet et al., 2015). Cole (2024) noted that sustained demand for elite genetics inherently conflicts with increasing inbreeding, making strict control of reproductive technologies practically impossible.

The impact of recessives alleles on fertility

Reproductive success depends not only on the genetic and functional quality of oocytes and semen but also on the embryo's genotype,

which—together with the maternal environment—critically influences pregnancy maintenance, especially in the presence of inherited defects leading to embryonic loss. Genetic defects are expressed when deleterious alleles occur in the homozygous state—a situation increasingly likely with rising inbreeding. When both parents carry a recessive allele, the embryo may inherit it in homozygous form, often resulting in very early embryonic mortality that can be misclassified as female fertility failure.

While selection can reduce the frequency of recessive defects, complete eradication is unrealistic; therefore, avoiding carrier-by-carrier matings remains essential. Genotyping enables carrier detection, and integrating this information into mating programs with advanced algorithms allows more effective mate allocation. Cole (2015) proposed incorporating the expected cost of genetic load by adjusting parent averages during mating decisions. Such tools help minimize harmful pairings, reducing defect expression and supporting long-term fertility and population health.

When a female's genotype is unknown—a common scenario—mating programs can use estimated carrier probabilities. In Canada, this has been routine since 2016 (CDN, 2016), with probabilities derived from test results, genomic haplotypes, and pedigree data. The accuracy of this approach depends on comprehensive genotyping and deep pedigrees (Lactanet, 2024).

Historically, eliminating carriers—especially bulls—was the primary strategy for controlling genetic defects, successfully removing conditions such as BLAD (Bovine Leukocyte Adhesion Deficiency) and CVM (Complex Vertebral Malformation). Genomic selection, however, has greatly expanded the detection of monogenic defects (VanRaden et al., 2011), and as the number of identified defects increased (Cole et al., 2025; Sahana et al., 2013), excluding all carrier males became impractical. Consequently, mating programs have become central to managing genetic defects.

Although selection cannot eliminate recessives entirely, it can markedly reduce their frequency. Many defect alleles now occur at <5% (Lactanet, 2019). Cole et al. (2025) reported that carrier frequencies declined by one-third in U.S. Holsteins and by half in Jerseys between 2012 and 2022, demonstrating strong long-term selection response.

New recessive defects continue to emerge, with Cole et al. (2025) providing an updated list—particularly extensive for American Holsteins. Widespread female genotyping has improved detection, commonly through identifying haplotypes lacking homozygotes—suggesting a lethal mutation. However, this method works only when all copies of a haplotype carry the causative variant, which is not always true, as shown by BLIRD (Bovine Lymphocyte Intestinal Retention Defect) and Muscle Weakness, where the absence of homozygotes is incomplete or inconsistent (Al-Khudhair et al., 2024, 2023; Dechow et al., 2022). In such cases, additional pedigree- and family-based validation is required.

Effective detection of emerging defects depends on systematic reporting of suspect calves and is strengthened by breeder awareness, coordinated collaboration, and dedicated reporting tools. Examples include those provided by the Irish Cattle Breeding Federation, such as a national congenital-defect reporting survey (ICBF, 2024) and an online Genetic Defects Gallery that enables farmers and veterinarians to document abnormalities (ICBF, 2025). In France, congenital genetic defects are monitored through the National Observatory of Bovine Abnormalities (ONAB), a joint initiative of INRAE (Institut National de Recherche pour l'Agriculture, l'Alimentation et l'Environnement; French National Research Institute for Agriculture, Food and Environment), breeding organizations and veterinary services, which has proven highly effective in detecting new defects and supporting their management in selection (Grohs et al., 2016). The success of identifying and managing emerging genetic defects depends on stakeholder coordination. In North America, informal but well-organized collaboration among farmers, breed associations, AI organisations and researchers has enabled early detection of new defects and their underlying mutations (Cole et al., 2025).

Chromosomal abnormalities and fertility

Another genetic factor that may masquerade as a fertility issue involves chromosomal abnormalities in embryos. Routine diagnostics for chromosomal aberrations have been available since the 1960s, but recent genomic advances provide new opportunities for detection (Switonski et al., 2025). Ryan et al. (2025) showed that dense SNP genotyping can reliably identify aneuploidies, thereby reducing costs associated with rearing infertile animals and unsuccessful breeding attempts. In their study, the prevalence of three specific aneuploidies ranged from 0.0004% to 0.0048%.

Advancing genetic progress to improve fertility also includes pre-implantation testing of embryos for chromosomal abnormalities. Bouwman and Mullaart (2023) demonstrated that such testing can be performed before implantation, reporting a 5% frequency of chromosomal abnormalities among 558 embryos.

Management of fertility

Role of reproductive biotechnology in breeding programs

Key reproductive biotechnologies have accelerated genetic progress in dairy cattle, beginning with the introduction of artificial insemination (AI) in the early 1900s, followed by semen freezing in 1949, embryo culture and sexing in the 1970s, and later in-vitro fertilization, cloning, and sperm sorting (Moore and Hasler, 2017). These technologies enabled rapid dissemination of superior genetics and made it possible to identify individuals with the highest breeding values. Historically, accurate sire evaluation relied on progeny-testing programs, in which bulls were assessed based on the performance of 50–100 daughters produced through widespread AI. This large number of AI-generated daughters has remained essential for maintaining robust reference populations used to estimate reliable genomic breeding values in modern dairy cattle populations.

Artificial insemination

By reducing the number of bulls required for breeding, artificial insemination enables very high selection intensity. The existence of “millionaire bulls,” each producing over one million semen doses, illustrates the efficiency of this system. Moreover, AI has facilitated international dissemination of genetic progress through evaluations coordinated by Interbull. In the genomic era, this process has become even more effective: submitting a bull's genotype to a national evaluation center allows the estimation of genomic breeding values, while initiatives such as the EuroGenomics consortium enhance genotype exchange and improve the accuracy and comparability of national genomic evaluations. The resulting genomic breeding values are publicly available.

The widespread use of AI also underpins modern reproductive management strategies, as it enables flexible allocation of semen types (conventional dairy, sexed dairy, and beef) according to genetic merit, fertility status, and herd replacement needs. This flexibility has become increasingly important with the expansion of sexed semen and beef-on-dairy strategies in dairy systems.

Embryo transfer

On the female side, reproductive biotechnologies such as ET and oocyte pickup have become integral tools for accelerating genetic gain by enabling earlier and more accurate identification of elite dams and by shortening the generation interval. Genomic selection further enhances these strategies by allowing breeders to target the most promising females and capitalize on Mendelian sampling variance by resolving genetic differences among full-sibs at an early stage, particularly when embryos are genotyped (Hirayama et al., 2008). These approaches strengthen both the dam–daughter and dam–son pathways, while also increasing selection intensity in female lines.

The use of ET has expanded rapidly in competitive breeding programs. In 2015, 41,921 embryo flushes and 32,636 oocyte collections were performed in U.S. cattle (Moore and Hasler, 2017). Globally, activity continues to increase: according to the International Embryo Technology Society, 1.9 million embryos were produced in vitro in 2023 (a 15 % rise from 2022), whereas 0.37 million were produced in vivo (a 6 % decline) (IETS, 2024). This expansion reflects both reduced costs and the strong incentives created by genomic selection, which increases the value of producing offspring from genetically elite females (Miles et al., 2023).

From an economic perspective, although insemination with sexed semen is roughly twice as costly as conventional insemination, purchasing an embryo may cost only slightly more than three times that amount (Kaniyamattam et al., 2018), further encouraging the use of ET. As ET becomes more widespread, its potential to accelerate the dissemination of genetic progress continues to grow (Crowe et al., 2021).

Sexed semen

Genomic testing is now widely used to stratify heifers according to genetic merit, ensuring that the top group receives sexed dairy semen for replacement production, a middle tier receives conventional dairy semen, and the lowest tier is bred to beef sires. Sexed semen is typically used first on heifers, given their higher genetic merit and superior fertility (Burnell et al., 2019). The extensive use of sexed semen not only contributes to an estimated 15 % increase in the rate of genetic progress (Weigel, 2004) but also enables more flexible and profitable herd management strategies, including dairy-beef crossbreeding. Since the use of reproductive biotechnologies in herd management entails additional costs and influences genetic gain, their application should be optimized. Simulation modeling by Ettema et al. (2017) demonstrated that incorporating genetic improvement is essential when evaluating the economic outcomes of reproductive strategies. Supporting this, Wellmann et al. (2024) showed that the optimal proportion of cows and heifers to be inseminated with each semen type depends on farm-specific characteristics, and that participation in herd genotyping programs is particularly advantageous for herds with low replacement rates.

Supported by major improvements in sperm-sorting technologies, modern sexed semen achieves female calf proportions exceeding 90 % and conception rates approaching 90 % of those obtained with conventional semen (Burnell et al., 2019). Its advantages—including increased production of replacement heifers, higher milk yields from dams delivering heifer calves (Hinde et al., 2014), and reduced stillbirth risk (Norman et al., 2010; Seidel and Garner, 2002)—generally outweigh its higher cost, with no adverse effects on gestation length, abortion rate, neonatal losses, or dystocia (Seidel and Garner, 2002).

In the United States, sexed semen has become the dominant semen type in dairy herds, with 9.9 million units sold in 2024—surpassing both beef-on-dairy (7.9 million) and conventional dairy semen (6.2 million) (NAAB, 2025). Similar trends are observed in the United Kingdom, where sexed semen accounted for 84 % of dairy semen sales in the year up to April 2024, reaching 88 % in Holsteins (AHDB, 2024).

The widespread availability of sexed semen has intensified the use of beef sires in dairy herds, making beef-on-dairy strategies an increasingly important component of modern reproductive management. This shift reduces the number of low-value dairy bull calves while enabling more efficient use of surplus reproductive capacity in dairy herds (Bolton and von Keyserlingk, 2021). In the United Kingdom, beef semen now accounts for 52 % of dairy-farm semen purchases (AHDB, 2024), and historically high beef prices have similarly increased the use of beef sires and beef embryos in the United States.

To support these strategies, genetic tools such as the Irish Dairy–Beef Index help identify beef bulls suitable for use on dairy females, balancing carcass value with calving performance and maternal traits (Berry et al., 2019; Berry and Ring, 2020). Available evidence suggests that beef-on-dairy matings have only negligible biological effects on reproductive performance.

Hormonal interventions in reproductive management

Herd management practices strongly influence reproductive performance and the rate of genetic progress, and they add complexity to the relationship between observed fertility and its genetic component. Importantly, the effectiveness of reproductive biotechnologies depends on sound day-to-day reproductive management (Ettema et al., 2017), which in many herds is supported by hormonal programs. When fertility problems become severe, the dam–daughter selection pathway breaks down and producers are forced to purchase replacements, increasing costs and reducing the herd's genetic gain by eliminating the opportunity to select future cow dams. By contrast, well-managed herds can maintain reproductive efficiency and fully benefit from selection and reproductive technologies.

Hormonal programs are widely used to manage reproduction in large dairy herds, particularly where heat detection is difficult or labour-intensive. Fixed-time AI (TAI) protocols synchronise ovulation, enabling insemination without oestrus detection, whereas oestrus-induction protocols rely more heavily on observation. Adoption is widespread: approximately 30 % of Canadian producers and around 70 % of U.S. cows receive hormonal treatments before first postpartum insemination (Brotzman et al., 2015; Oliveira Junior et al., 2021a). While these programs improve reproductive efficiency, they can mask natural fertility phenotypes. Cows enrolled in TAI are inseminated on predetermined days, regardless of ovarian status, potentially distorting traits such as days to first service and pregnancy rate (Wiltbank and Pursley, 2014).

Initially, Lucy (2019) reported minimal differences in bull rankings between the United States—where hormonal programs are widely implemented—and Ireland, where their use is limited. However, simulation results by Oliveira Junior et al. (2021a) demonstrated that including records from cows under TAI can bias fertility breeding values, with bias increasing in proportion to the number of treated animals. Analyses of Canadian Holsteins confirmed this concern: Lynch et al. (2021) showed that treating TAI as a fixed effect does not fully eliminate evaluation bias. Furthermore, Oliveira Junior et al. (2022) found that fertility expressed under TAI is genetically distinct from fertility expressed under natural estrus detection, with genetic correlations of only 0.73 for first service to conception, 0.89 for calving to first service, and 0.91 for DO. These results indicate that the two management contexts do not measure identical biological traits and that fertility records collected under hormonal synchronization require explicit modeling to avoid bias in breeding value estimation.

Management of heat stress

Although many cows exhibit reduced fertility under elevated temperature–humidity conditions, substantial individual variation in heat-stress sensitivity exists and is partly genetically determined (Bohmanova et al., 2007). During periods of high heat load, inseminations are commonly postponed due to declining conception rates, and clear genotype-by-environment interactions have been demonstrated (Bohmanova et al., 2008; Campos et al., 2022). Long-term selection for production traits has increased thermal susceptibility in modern Holsteins, and resistance to heat stress is favourably correlated with fertility. Even in temperate regions such as Canada, cows increasingly display sensitivity to elevated temperatures (Campos et al., 2022). Recent Canadian evidence indicates that heat stress also modifies the response to hormonal reproductive interventions, with most fertility traits showing increased sensitivity to temperature–humidity load when synchronization protocols are applied (Dodd et al., 2025). Enhanced cooling strategies mitigate production losses (Collier et al., 2012), yet management-based interventions partly explain why routine national-scale evaluations for heat-stress resistance have been implemented only in Australia (Nguyen et al., 2016). The feasibility of such evaluations was shown two decades ago, when Oseni et al. (2004)

demonstrated genetic evaluation for DO under heat stress. However, management strategies have intrinsic limits; once these are exhausted, more permanent, genetically anchored solutions become necessary. Recent advances—such as the U.S. single-step genomic model for heat-stress sensitivity (McWhorter et al., 2023)—indicate that national genomic evaluations for heat-stress resilience are now technically feasible.

Delaying breeding after calving as part of reproductive management

Management decisions can also obscure genetic signals in fertility traits through intentional modifications of the reproductive schedule. One such example is the extension of the VWP. Studies indicate that prolonging the CI can benefit milk producers by improving both milk production and fertility outcomes (Edvardsson Rasmussen et al., 2023; Niozas et al., 2019). Edvardsson Rasmussen et al. (2024) demonstrated that selecting primiparous cows based on predefined criteria—such as high genomic merit for persistency—can support extended lactations that increase yield and improve fertility. However, variation in VWP across herds or seasons affects interval-based fertility traits and may weaken the accuracy of genetic evaluations unless explicitly modelled (VanRaden et al., 2004). To address this, Chang et al. (2007) proposed a model that simultaneously estimates VWP and predicts sire breeding values for pregnancy rate, eliminating the need to collect farmer-reported VWP data by deriving estimates directly from reproductive records.

Relatively inexpensive management-based approaches to improving fertility have allowed producers to prioritize production traits while applying limited selection pressure on fertility for many years. Misztal and Lourenco (2024) argued that in situations where selection for fitness traits is slow or costly, and where management interventions remain effective, prioritizing management over genetic selection may be economically justified. Nonetheless, the capacity of management interventions is finite, and long-term progress ultimately depends on genetic solutions that reduce the reliance on intensive reproductive management.

Opportunities and challenges of breeding programs

Fertility indicator traits and new phenotyping approaches

New phenotyping approaches provide opportunities not only for direct genetic selection on fertility, but also for indirect selection based on biologically and management-relevant indicator traits. Contemporary fertility management extends beyond hormonal protocols and conventional AI to include advanced pregnancy diagnosis, automated estrus detection and precision-livestock tools that continuously monitor activity, rumination, feeding, and body temperature (Stevenson and Britt, 2017). Assisted reproductive technologies such as ET also offer indirect benefits for fertility, particularly under heat stress. Elevation of temperature impairs oocyte competence, fertilization, and very early embryo development in the oviduct (Al-Katanani et al., 2002; Hansen, 2020; Sartori et al., 2002). Because ET bypasses these highly heat-sensitive stages by transferring more advanced embryos, it can partially mitigate summer infertility (Crowe et al., 2021), and its use is increasing in dairy herds (Miles et al., 2023), especially when combined with genomic testing, sexed semen and beef-on-dairy strategies (Basiel et al., 2025).

Milk mid-infrared (MIR) spectra, routinely collected in milk recording, represent a promising resource for indirect selection on fertility, as they capture subtle shifts in milk composition that mirror energy balance, inflammatory status and key physiological transitions throughout the reproductive cycle. Mid-infrared predictions therefore provide insight into the metabolic and inflammatory conditions underlying the resumption of ovarian activity. For example, milk fatty acid profiles related to body-tissue mobilization have been associated with CI (Bastin et al., 2012), and MIR-derived traits can predict estrous phase

and expected estrus date (Toledo-Alvarado et al., 2018).

Precision-livestock technologies further expand the suite of fertility-related phenotypes. Integrated systems allow remote recording of activity, BCS and health indicators (Lucy, 2019). Traits such as the interval from calving to first elevated activity, derived from accelerometer data, are heritable (Fleming et al., 2019; Heringstad and Wethal, 2023; Ismael et al., 2015) and strongly correlated with traditional fertility measures like the interval to first insemination. Nevertheless, heritabilities of estrus length and estrus expression remain low (<0.05 ; Ismael et al., 2015), and many cows ovulate without overt estrus (Sauls et al., 2017), underlining the value of accurate automated detection (Cerri et al., 2021) and the potential benefits of selecting for improved estrus expression (Lucy, 2019).

A growing set of novel indicator traits may support indirect genetic improvement of fertility. Anogenital distance (AGD) is strongly associated with fertility performance in heifers and cows (Carrelli et al., 2021; Gobikrushanth et al., 2017), and shows relatively high heritability ($h^2 \approx 0.39$; Dodd et al., 2025), making it a promising candidate for GS. Similarly, the reproductive tract size and position score (SPS) is favorably correlated with fertility and shows no antagonistic correlation with production (Martin et al., 2022). Disease-resistance traits, particularly those related to reproductive pathogens such as enzootic bovine leukosis, also show favorable genetic correlations with fertility, and heritable susceptibility to reproduction-impacting diseases such as bovine viral diarrhoea (BVD) and infectious bovine rhinotracheitis (IBR) has likewise been demonstrated (Bongers et al., 2025; McClure et al., 2014). Newly introduced resilience traits, such as stability and recovery of lactation curves, are heritable and exhibit favorable correlations with fertility (Meijer et al., 2024). Although twinning is an undesirable outcome with strong negative consequences for fertility, twinning rate itself is heritable with limited genetic antagonism to production, and the major loci identified to date explain only a modest proportion of its genetic variability—for example, the key BTA11 region accounts for approximately 0.6 % of variance in deregressed breeding values in Irish Holstein-Friesians but up to ~16 % of the genetic variance in Swiss Holsteins—indicating that selection against twinning remains feasible but will require polygenic rather than locus-specific strategies (Katende et al., 2025; Kirkpatrick and Berry, 2025; Widmer et al., 2021).

There is also increasing emphasis on phenotypes directly reflecting the biological underpinnings of fertility. Genetic correlations between uterine health and embryo survival (Carthy et al., 2015), and between heifer fertility breeding values and earlier puberty or higher pregnancy rates (Meier et al., 2021), point to the value of earlier, biologically grounded predictors of lifetime fertility. High-fertility cows appear to produce fewer chromosomally abnormal oocytes (Chasi Olivares et al., 2025), and traits such as antral follicle count (AFC) and circulating anti-Müllerian hormone (AMH) offer repeatable, biologically meaningful indicators of ovarian reserve. AMH is particularly attractive because of its relatively high heritability (Nawaz et al., 2018; Walsh et al., 2014) compared with other physiological fertility indicators (Ismael et al., 2015; Parker Gaddis et al., 2014; Tarekegn et al., 2019), although associations between AFC and fertility are not fully consistent across studies (Alward et al., 2023).

The main bottleneck for most of these novel traits is the cost and logistics of large-scale, standardized data collection. While emerging biosensing technologies could help bridge this gap—for example through real-time health alerts from intraruminal sensors enabling continuous biometric data streams (Rodriguez et al., 2025)—the value of new fertility phenotypes will ultimately depend on demonstrating that they capture biologically meaningful variation beyond what is already explained by existing fertility traits. In practice, only phenotypes that are biologically interpretable, heritable, scalable and robust across management systems are likely to be integrated into routine genetic evaluations, making rigorous trait definition and validation essential to ensure that new indicators enhance rather than complicate fertility-improvement strategies.

Optimizing and expanding genetic evaluation of fertility

Opportunities for improving genetic gain in fertility depend not only on trait definitions and novel indicators but also on optimized evaluation models for both females and males. Genomic selection has transformed the use of young bulls, allowing their widespread deployment before field fertility is known. Because traditional bull fertility indices, such as SCR, require large numbers of insemination records, genomic prediction offers a means to accelerate improvement in male fertility despite low heritabilities (Fortes et al., 2013). Large datasets show substantial between- and within-bull variation in semen-quality traits with low-to-moderate heritabilities (Gebreyesus et al., 2021; Sali-miyekta et al., 2023), supporting their inclusion in multi-trait evaluations. Although pooled (heterospermic) semen can yield slightly higher conception rates than the average of the contributing sires, evidence from DeJarnette et al., 2004 indicates that its performance does not exceed that of the best individual sire and therefore offers limited practical value as a fertility-enhancing strategy. Bull-level differences have also been demonstrated for embryo quality (O'Callaghan et al., 2021) and for fertility of sexed semen (Burnell, 2019), reinforcing the need for explicit genomic evaluation of male fertility. As with female fertility, advancing reproductive maturity and enabling earlier use of young bulls could further shorten the generation interval and accelerate genetic gain, provided that genomic predictions of male fertility are sufficiently reliable. To enable genomic evaluation of bull fertility, a suitable reference population is required. Rezende et al. (2020) demonstrated that pooling data across countries—specifically by integrating fertility records from the United States and Australia—can support the development of a robust reference population and improve the accuracy of genomic predictions for bull fertility.

Effective evaluation requires complete data. Recording confirmed conception dates, semen type (conventional vs sex-sorted), ET events and semen batch identifiers can increase the accuracy of models by accounting for semen processing, bull age and ejaculate quality (DeJarnette et al., 2010; Gebreyesus et al., 2021; Miles et al., 2023). In parallel, growing evidence that several semen-quality traits—such as post-thaw motility, sperm viability and pre-freeze sperm concentration—are moderately heritable and strongly correlated with service-sire fertility demonstrates that male fertility can itself be evaluated genetically, offering a clear pathway for incorporating semen-quality traits into routine breeding value estimation (Gebreyesus et al., 2021). However, practical implementation may be challenging because commercial AI organizations often manage dose-to-dose variation through internal quality-control procedures, meaning that raw laboratory data needed for robust evaluations are not always available at the population level.

Multi-trait models that jointly evaluate age at first insemination, calving-to-conception intervals, non-return rates, calving traits and calf survival have been successfully applied in Holsteins (Jamrozik et al., 2005), and can be extended to incorporate novel physiological or sensor-derived traits. Multi-breed genetic evaluation models can also help identify beef sires suited for dairy herds and optimize beef-on-dairy strategies (Splittorff et al., 2023), but although some fertility benefits have been observed in Holstein crossbreds, these effects are system-dependent and do not replace within-breed genetic improvement as the main source of long-term progress (Heins et al., 2006).

Single-step genomic evaluations, which combine pedigree, phenotype and genomic data in a unified model, offer improved accuracy for low-heritability traits, and can accommodate animals of different genetic backgrounds (Tabet et al., 2025). Many European countries now use single-step approaches in routine Holstein evaluations (Interbull, 2025). Harmonizing trait definitions and evaluation models across countries further enhances accuracy by enabling larger reference populations and international use of breeding values (Mota et al., 2021). Initiatives such as the EuroGenomics “Golden Standard” have defined best practices for data recording, editing, modelling and publication of

fertility traits, aligned with Interbull recommendations (Eurogenomics, 2025), although full implementation remains costly and technically demanding.

Beyond traditional mixed models, machine-learning approaches are increasingly applied to complex fertility datasets. They have been used to integrate biomarkers and transcriptomic data for predicting uterine receptivity (Rabaglino and Kadarmideen, 2020) and pregnancy success after AI (Hoorn et al., 2024). These methods may extract additional predictive signal from high-dimensional data but require careful validation and integration with existing genetic evaluation frameworks.

Genome-wide association studies (GWAS)

Genome-wide marker availability has enabled both GS and GWAS, with the latter providing a route to dissect the complex genetic architecture of fertility and to identify potential targets for indirect selection. Fertility traits are strongly polygenic with low heritabilities and substantial environmental sensitivity, so major QTL are rare and often population-specific (Huang et al., 2010; Peñagaricano et al., 2012; Rossoni et al., 2023; Sahana et al., 2010). Across multiple large GWAS, only one robust QTL on BTA18 has been consistently identified for female fertility, and most studies report study-specific signals that are difficult to replicate (Ma et al., 2019). Nevertheless, marker panels derived from candidate-gene approaches have improved the reliability of fertility evaluations in some settings more than further increases in SNP density alone (Cochran et al., 2013a, 2013b; Ortega et al., 2016; VanRaden et al., 2013).

Future progress will rely on integrating GWAS with functional genomics. Rich genomic resources, combined with transcriptomic and regulatory data, can help to map GWAS signals to causal genes and pathways (Hosseinzadeh et al., 2025), including for male fertility traits and testis-specific genes (Peñagaricano, 2024). Livestock initiatives modelled on the human GTEx project aim to connect genetic variants with tissue-specific gene expression at scale (Fang et al., 2025; Teng et al., 2024). Copy-number variation regions, identified through GWAS studies, associated with fertility and reproductive-health traits further illustrate the potential of structural variants to explain part of the genetic variance (Rojas De Oliveira et al., 2024).

In addition, GWAS can reveal genotypes that modify responses to fertility treatments, suggesting paths for more individualized reproductive management. For example, specific genotypes associated with improved response to hormonal protocols have been linked to higher pregnancy rates (Zolini et al., 2019). However, such findings also highlight that the widespread use of hormonal treatments, if not explicitly modelled, may bias fertility evaluations and alter allele frequencies in unintended ways (Berry et al., 2016; Cole and Hansen, 2020).

The role of epigenetics and the microbiome

Fertility is influenced not only by DNA sequence but also by epigenetic mechanisms that modulate gene expression without changing the underlying genome. DNA methylation, histone modifications, non-coding RNAs and chromatin structure are sensitive to environmental factors and can contribute to transgenerational phenotypic variation (Xavier et al., 2019). Increasing evidence suggests that both paternal and maternal epigenetic marks, including those in gametes and early embryos, are associated with fertility-related traits and responses to reproductive technologies (Fang et al., 2019; Rabaglino et al., 2023; Wang et al., 2017).

Epigenetic differences have been documented between bulls with contrasting conception rates, including distinct methylation patterns in sperm and altered transcriptomes in preimplantation embryos (Capra et al., 2025; Kropp et al., 2017). Key environmental drivers include parental age at puberty, maternal metabolic status at conception and in vitro culture conditions (Wu and Sirard, 2020). Although causality

remains difficult to establish, recent work suggests that epigenetic biomarkers may help predict postpartum fertility disorders (Bouzeraa et al., 2025), indicating potential for indirect selection or early risk stratification.

The microbiota of the bovine reproductive tract is another emerging dimension of fertility. Microbial communities in both males and females are associated with fertilization, implantation and pregnancy maintenance (Luecke et al., 2022). Their composition depends on diet, environment, hormonal status, health and management (Gupta et al., 2024), and partial maternal transmission to offspring has been reported (Adnane and Chapwanya, 2022). Variation in reproductive-tract microbiomes has been linked with multiple fertility outcomes, and recent results suggest that microbiome modulation can increase the probability of conception at first AI (Figueiredo et al., 2024). Microbiome-derived indicators may ultimately complement genetic and management information in fertility prediction models (Gupta et al., 2024).

Breeding beyond reproductive limits

Classical strategies to accelerate genetic gain, such as MOET schemes and modern GS, operate within natural reproductive and developmental constraints: selected animals must still grow, reach puberty and produce gametes. In contrast, emerging concepts aim to circumvent biological generation limits. Oocyte retrieval from very young heifers—or even fetuses—followed by in vitro fertilization demonstrates that substantially shorter generation intervals are biologically feasible (Betteridge et al., 1989; Galli et al., 2001). Building on this principle, Kasinathan et al. (2015) proposed strategies in which fetal cells are subjected to GS and then used for cloning, potentially reducing the generation interval to about seven months.

More radical proposals envision in vitro breeding systems based on embryonic stem cells (ESCs) and in vitro-derived gametes (Goszczyński et al., 2019). In such a scenario, embryos would provide ESCs for GS, and selected ESC lines would be differentiated into gametes to produce the next generation, theoretically reducing generation intervals to 3–4 months. While conceptually attractive, robust protocols for deriving and propagating bovine ESCs across laboratories are still lacking, and the epigenetic stability and long-term fitness of animals produced through such cycles remain uncertain.

These in vitro breeding concepts raise additional challenges. Accuracy of GS may decline if generation intervals become much shorter than the time required to collect phenotypes from reference populations (Pszczola et al., 2019). Economic feasibility is unclear, and legal or ethical constraints may restrict the use of animals produced through intensive in vitro manipulation, particularly if they are classified as genetically modified organisms.

Genome editing

Genome editing is a more immediate DNA-based technology with potential to complement GS fertility-focused breeding programs. By directly increasing the frequency of favorable alleles, especially those that are rare or absent in elite germplasm, editing can accelerate genetic progress within a single generation (Johnsson et al., 2019). The approach is particularly suited to traits controlled by major genes, such as the polled locus, where relying solely on selection entails opportunity costs and increased inbreeding (Mueller et al., 2019). Similar arguments apply to alleles conferring disease resistance, including those related to mastitis tolerance (Bengtsson et al., 2022; Liu et al., 2022; Wang et al., 2022), which can indirectly improve fertility by reducing disease burden.

Genome editing can also target alleles that directly influence reproductive performance, for example by enhancing thermotolerance through the SLICK allele without compromising broader genetic merit (Zayas et al., 2025), or by modifying variants with demonstrated effects on fertility (Eenennaam, 2019; Ideta et al., 2016). Related advances, such as surrogate sire technology (producing males that generate sperm

derived from elite donor germ cells), also point toward a future in which dissemination of genetics may become decoupled from traditional reproduction and local environments. Intensive use of editing in elite animals, however, increases the risk of homozygosity and requires careful inbreeding management (Jenko et al., 2015). Simulation studies suggest that well-designed, editing-intensive breeding schemes—often relying on high reproductive efficiency—can still maintain acceptable inbreeding levels (Gonen et al., 2017; Mueller and Van Eenennaam, 2022).

For complex traits such as fertility, editing would likely need to be multiplexed, targeting several loci simultaneously (Johnsson et al., 2019; Sonstegard et al., 2024). The success of such approaches depends on ongoing discovery of commercially relevant targets through GWAS and functional genomics. Practical constraints include the time and cost associated with generating edited cell lines, screening edits, and producing viable clones for breeding use (Cole et al., 2025).

From a societal and regulatory standpoint, genome editing may be more acceptable than classical transgenesis because edits often mimic alleles that could arise naturally or through selection (Eenennaam, 2019; Gaj et al., 2016). Several countries currently permit commercialization of gene-edited, non-transgenic animals under non-GMO classifications (Ledesma and Van Eenennaam, 2024). Nonetheless, public perception, ethical considerations and region-specific regulations will strongly influence adoption in dairy breeding.

Toward sustainable genetic improvement

Sustainable dairy breeding requires balancing productivity, fertility, health, robustness, environmental impact and social acceptance. Female fertility is central to this balance because it affects reproductive efficiency, longevity and emissions per unit of milk. Historically, selection for production traits contributed to declining fertility, and although GS has allowed breeders to reverse this trend, the genetic response in fertility still lags behind that of production traits. Recent work indicates that genomic breeding values for date-based fertility traits can predict reproductive performance with similar accuracy to production traits in some systems (Bengtsson et al., 2020; Lima et al., 2020; Toghiani et al., 2024), while other studies report weak or no correspondence between genomic evaluations and realized fertility (Strabel, 2025). This discrepancy underlines the need for continuous monitoring of both phenotypic and genetic trends in fertility.

The genetic correlations between fertility and production are generally unfavorable but can be nonlinear and trait-specific. In German Holsteins, reproductive disorders show low heritabilities and heterogeneous genetic correlations with milk yield, varying with herd production level (Schwarz et al., 2025). Stronger selection enabled by genomic tools may further reduce heritabilities and intensify unfavorable correlations, as already reported in pigs and broilers (Hidalgo et al., 2021; Richter et al., 2024). Emerging methods for variance-component estimation in very large, genotyped populations (Misztal and Gowane, 2025) will be important to track these changes and to avoid unintended deterioration of reproduction.

Management practices, particularly hormonal reproductive programs, also shape the trajectory of fertility. Extensive use of hormones can successfully reduce DO and culling for infertility, improving phenotypic fertility trends even when genetic merit changes slowly. A further consideration is that extensive hormonal support may allow cows with inherently lower reproductive ability to remain in the breeding population, potentially weakening natural culling pressure on fertility. Reliance on such programs may reduce the perceived economic value of fertility traits in selection indices and is increasingly scrutinized by veterinarians, consumers and regulators (Higgins et al., 2013; Sax, 2017; Wicaksono et al., 2023). Refining reproductive strategies to maintain fertility and profitability while reducing blanket hormone use would better align practice with societal expectations (Chebel et al., 2025).

Longevity presents another trade-off. Improved reproduction, health and housing can extend productive life and reduce emissions intensity, but farmers may still choose relatively high voluntary replacement rates to capitalize on genetic progress by introducing superior young animals (Christen et al., 2022). Shorter cow lifespans can thus reflect economically rational decisions that are not fully aligned with goals of maximizing biological resilience or minimizing environmental impact.

New technologies such as genome editing, advanced phenotyping and reproductive biotechnologies offer additional tools to improve fertility within a sustainability framework. Yet their adoption depends on farmer attitudes, economic incentives and regulatory environments. Surveys indicate that openness to novel technologies is higher in larger herds and among younger farmers, while the wider population shows a spectrum of views ranging from cautious interest to skepticism (Crowe et al., 2021; Gargiulo et al., 2018; Keyserlingk et al., 2024).

Conclusions

Fertility remains one of the most biologically complex and genetically constrained components of dairy cattle improvement, and its response to selection depends on the alignment of genetic, biological and management domains. Historical declines in fertility were driven not by limitations of evaluation methodology—now well developed in the genomic era—but by phenotypes that capture only a limited fraction of reproductive biology and are strongly influenced by environment and management. At the same time, increasing selection intensity has exacerbated inbreeding and recessive load, while widespread reliance on management interventions, particularly hormonal synchronization, can mask genetic variation and weaken long-term selection responses. Together, these factors illustrate that fertility is constrained less by the tools of genetic evaluation than by the way biological information is generated, recorded and expressed.

Looking forward, the main opportunities for sustainable fertility improvement lie in coordinated progress across domains rather than in any single technology. Biologically meaningful and scalable phenotyping, including novel indicator traits and sensor-based data streams, must be coupled with evaluation frameworks that explicitly accommodate reproductive technologies, management heterogeneity and both female and male fertility. Management will continue to play an essential role, but long-term gains will depend on strategies that expose—rather than substitute for—the genetic signal. As emerging tools such as genome editing and advanced reproductive biotechnologies expand the technical possibilities of improvement, their successful application will ultimately depend on integrated industry planning and societal acceptance. Only under such alignment can fertility respond consistently to selection and remain a cornerstone of productive, resilient and sustainable dairy breeding systems.

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CRediT authorship contribution statement

Tomasz Strabel: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **John B. Cole:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no competing interests, nor any other interests that could be perceived to influence this paper.

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