Selecting for female fertility: What can be learned from the dairy experince

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Introduction

Genetic improvement programs in dairy cattle have until recently focused on increasing net profit by increasing gross income per cow, rather than reducing costs of production [1]. Strong selection pressure on yield traits coupled with management practices aimed at maximizing production may have resulted in undesirable side effects related to decreased fitness [2]. These concerns have been confirmed by work on reproductive efficiency done among others by Lucy [3] and VanRaden et al. [4]. There are strong motives for including reproduction in selective programs, both economical and welfare related [5].

Female fertility cannot be easily defined as a single trait as it comprises different aspects. Some of these aspects are related to the prompt resumption of cyclicity and the showing of recognizable estrous behavior, while others are related to the ability of the cow to become (and remain) pregnant with a limited number of inseminations [6]. In addition, cows should have good calving ability and give birth to viable calves [5].

A relevant body of literature now links selection for production to a loss of reproductive fitness, health, and longevity in several breeds [7], [8], and unsatisfactory reproductive performance is a primary reason for culling for the first three lactation in the USA dairy population [9].

Factors affecting cows' fertility

Several factors are responsible for good (or bad) fertility in cows. Although in the following section we have separated some for sake of simplicity it should be kept in mind that most of these elements are intrinsically related and exert some effect on each other.

Management: Management represents one of the factors with largest effect on female fertility. In a 2009 study Tsuruta and coworkers [10] reported differences in fertility parameters among large and small dairy operations. The authors found an average difference of 7 days in favor of large herds for calving to conception (days open), and days to first second and third service (17, 22, and 24 respectively). In contrast conception rates (overall, at first, second, and third insemination) were higher for smaller herds with advantages of approximately 5% in all cases. The largest influence exerted by management practices on fertility can be linked to the conditioning of cows around parturition. Negative energy balance (NEB) at the beginning of lactation is responsible for an increase in metabolic diseases, reduced immune function, and overall decreases in fertility [11]. Body condition scores (BCS) is the most easily applicable tool to monitor and manage the metabolic status of cows around parturition. Cows with low levels of BCS at parturition suffer from extreme NEB with a reduction of ovulation rate, increased calving to first insemination, and increased calving intervals [12]. Over-conditioned dry cows are more likely to suffer from ketosis and fatty liver, both of which may suppress immunity directly or through an excessive negative energy balance route [13]. Because of these inter-relationships, unfavorable energy balance in the transition cow regularly results in cascade effects that increase the incidence of infectious diseases, production diseases, and consequently reduce fertility.

Environmental effects: Several environmental components affect female fertility. Among these heat stress is particularly significant. Summer heat stress is a main factor related to low conception rate in high producing dairy herds in warm areas worldwide [14]. Under heat stress, production and fertility decrease and animals have a decreased chance of survival [15]. Ravagnolo and Misztal [16] found for example, correlations between non return rate at 90 day and heat tolerance of -0.95. Furthermore, Garcia-Ispierto et al., [14] found that the likelihood of conception rate for Spanish Holstein Friesians increased significantly by factors of 1.48, 1.47, 1.5, and 1.1 for Temperature Humidity Indexes (THI) classes <70, 71–75, 76–80, and 81–85 on Day 3 before artificial insemination (AI), and by factors of 1.73, 1.53, 1.11, and 1.3 on the insemination day, for THI classes <70, 71–75, 76–80, and 81–85.

Incurrence of diseases: While in most cases disease losses are quantified through their direct costs associated to production loss, increased culling rate and treatment costs, their importance go beyond these direct effects and often involve the costs related to a decrease in fertility.

Mastitis: Mastitis is an inflammation of the mammary gland and is responsible for reduced milk production and milk quality, increased involuntary culling rates, and discarded milk [17]. Cows experiencing clinical mastitis before first postpartum artificial insemination (AI) have a greater days not pregnant (DNP) compared with uninfected cows [18]. Moreover, cows experiencing mastitis between the first AI and pregnancy confirmation have greater services per conception (S/C) and DNP compared with cows without mastitis [18].

Lameness: Lameness can be defined as an abnormal gait due to leg or foot problems [19] and includes several different foot lesions. Lameness has a detrimental effect on herd productivity, second only to mastitis [20]. Negative effects of lameness include a decrease in milk yield [21], [22] and fertility [23] and an increase in risk of culling [24].

Uterine diseases: Uterine diseases are a family of diseases (metritis, endometritis) associated with abnormal post-partum events. These diseases are associated with sub-fertility and infertility and are characterized by longer intervals from calving to first insemination or conception for affected animals, and more cows culled for failure to conceive in a timely manner [25]. As an example, LeBlanc et al. [26] showed that service conception rate was lower for cows with endometritis (29.8% vs. 37.9%), with longer median calving to conception interval (151 vs. 119 days) and with more diseased animals culled for failure to conceive (6.7% vs. 3.8%) than unaffected animals.

Parity: Several authors have reported a general decrease in fertility performance with increase of parity number. VanRaden at al., [4] reported phenotypic trends in days open from first to fifth parity from 1965 to 2000. For the period reported days open increased with parity order, with differences of approximately 20 days between first and fifth lactation. Similar results have been reported for number of inseminations [7], [27], [28].

Production level: High producing cows tend to be less fertile and this prolongs the length of calving interval as well as the rate of involuntary culling [29]. Genetic antagonism between yield and fertility is often indicated as the major factor leading to declines in reproductive performance [30], [31], [32]. This antagonism is related to higher energy utilization from the mammary gland in early lactation to sustain elevated production, leading to an amended hormonal and metabolic profile, which in turn exerts a negative effect on ovulation rates, estrous behavior, and embryo establishment [33]. Low fertility is therefore at least in part a manifestation of the cow's inability to cope with the metabolic demands of high production.

Breed: Breed is a significant contributor to cow fertility. Campos et al., [34] reported differences in calving to conception and calving interval between Holstein and Jersey cows, with a difference in favor of the Jersey breed of 39 and 19 days for days open and calving interval, respectively. Similarly, Grosshans et al., [35] compared calving to conception and calving intervals between Holstein and Jerseys and found shorter intervals of 5 and 3 days in favor of Jerseys for days open and calving intervals, respectively. Inchaisri et al., [27] estimated the probability of success at first insemination in relationship to the proportion of Holstein or Dutch red and white genes present. Percentages of success ranged from approximately 37% for purebred Holstein to 43% for purebred red and white with a linear increase in success rate as a function of the increase of red and white genes. VanRaden et al., [4] reported values of Daughter Pregnancy Rate for Ayrshire, Brown Swiss, Guernsey, Holstein, Jersey and Milking Shorthorn calculated with a multi-breed animal model. Daughter pregnancy rate is one the measures of fertility reported by the USDA Animal Improvement Program Laboratory (AIPL), and represents the percentage of non-pregnant cows that become pregnant during each 21-day period. The authors reported average predictive transmitting abilities (1/2 of the Estimated Breeding Value) of, -0.5, 0.1, -0.8, -0.2, -0.3, +0.2, for the different breeds, respectively.

Breeding for increased fertility

Traits definition: A univocal definition of fertility is a complicated (and perhaps vane) exercise. Pryce et al., [31] describe fertility as “The accomplishment of pregnancy at the desired time”, while Hyppanen and Juga [36] refer to it as “The ability to produce a living offspring during an economically and physiologically approved period”. Darwash et al. [37] frame fertility as the “Ability of the animal to conceive and maintain pregnancy if served at the appropriate time in relation to ovulation”. Finally, for Groen et al., [6] “Female fertility can be defined as the ability of the cow to return on heat within an acceptable period, to show the heat in a proper manner and to become pregnant with a minimum number of inseminations”. Although several authors place more or less emphasis on some specific aspects of fertility, at least two main components can be readily identified [38]:

- ✓ The success at a particular event (insemination, pregnancy)
- ✓ The elapsed time to that particular event

The majority of traits currently measured and employed in selection programs fall in one of these two categories.

- ✓ *Conception rate:* Can be defined as the outcome (success/failure), for every insemination, validated by pregnancy check or calving.
- ✓ *Number of insemination to conception:* Is the number of services needed to achieve pregnancy.
- ✓ *Calving Interval:* Describes the difference, in days, between two subsequent calvings.
- ✓ *Interval from calving to first service:* Is the difference, in days, between calving and the next breeding.
- ✓ *Interval from 1st service to conception:* Is the difference, in days, between first and last service (validated by pregnancy check or subsequent parity)

To these general categories, more specific definitions can be added and additional parameters can be considered. For example, hormonal profiles can be employed in characterizing fertility.

Lamming and Bulman [39] recognized that "Progesterone profiling provides a more objective method for tracking reproductive events in dairy cows" and more recently, work on this area has been presented by Pollot and Coffey [40], and Petersson et al. [41], [42]. Direct measures of fertility are difficult to obtain and data quality is often a challenge. Therefore several correlated traits are often employed as proxy measures of fertility. Several authors have proposed the measure of energy balance as a reliable indicator of the fertility status of individual cows. Energy balance can be monitored directly or through indirect measures. The most widely used measure of energy balance in cows is the Body Condition Score (BCS), although more recently the use of milk parameters such as protein/fat ratio [43] and milk urea has been proposed [44]. A summary of the most common measures of female fertility is reported in Table 1.

Data structure: Several challenges arise from the use of fertility traits related to data quality and availability. Calving interval is the trait most easily measured and is only marginally influenced by data quality when compared to other direct measures of fertility such as conception rate or number of inseminations to conception. However, it is not available for individuals culled before subsequent calving for fertility or other problems, leading to overestimation of reproductive performance. Moreover, calving interval is a late measure of fertility as it is available almost one year after the beginning of estrus activity with a delayed publication of breeding values. Several alternative measures have been proposed as early-recording indicators for fertility [12].

Box 1: The challenges of selecting for fertility traits:

Biological:

- ✓A mixture of traits

Structural and logistics:

- ✓Data Availability
- ✓Data Quality

Modeling:

- ✓Binary/Ordinal
- ✓Unequal variance
- ✓Censoring

Selection:

- ✓Low h^2
- ✓Antagonistic effect on production traits

Non-return rate at 56 days after first service (NR56) is the most widely used trait in genetic improvement of fertility in dairy [45], [8]. An important limitation of this trait is that it considers successful all terminal services without the validation of a subsequent calving date. On the other hand, NR56 provides a fast evaluation for fertility where the subsequent calving has not (yet) occurred.

The use of direct measures of fertility other than calving interval could lead to more timely results in breeding programs, provided that phenotypic data are reliable and that they are modeled correctly. One of the major limitations with fertility traits is that female fertility is not fully represented by a single trait but it is rather a complex of traits including non-normal and categorical traits. Conception rate and the number of inseminations are categorical and highly skewed. The intervals (parturition-first insemination, first insemination-conception, and parturition-conception) are conceptually based on a categorical number of estrus cycles and are again characterized by a highly asymmetrical distribution. Furthermore, not all the cycles lead to an insemination (voluntary waiting period, non observed estruses, health problems, etc.), not all inseminations result in a conception (infertility), and not all conceptions lead to a parturition (abortions), thus confirming the complexity of defining reproduction efficiency.

Finally, the beginning and end of each estrus cycle are not regularly recorded at the population level and insemination and parturition information is sometimes lacking as well (censored data). Modeling the intervals in terms of number of potential 21-d cycles and the use of censored threshold models has been proposed to overcome some of these limitations [46].

Table 1. Fertility traits definition.

Trait	Variable	Definition
Success traits:		
Conception at *x* service	Binary [0/1]	The outcome of an insemination validated by calving data
Non-return at *n* days after *x* service (n=56-60-70-90)	Binary [0/1]	The outcome of an insemination validated by the occurrence of a second breeding within *n* days
Number of insemination to conception	Count [1,2…n]	The number of services needed to achieve pregnancy
Conception rate	Continuous [0…1]	1/INS
Non-return rate at *n* days after *x* service		1/NRn
Interval traits:		
Days from parity to first heat	Continuous (days)	The days from calving to the first observed heat (by farmer)
Voluntary waiting period	Continuous (days)	The number of days intentionally left by the farmer before the re-start of breeding
Days from parity to first service	Continuous (days)	The days from calving to the first service
Days from first service to conception	Continuous (days)	The days from the first to the successful service (or the last service if no calving is available)
Days from parity to conception	Continuous (days)	The days from calving to the successful service (or the last service if no calving is available)
Calving interval, in days	Continuous (days)	The number of days between 2 subsequent calvings
Endocrine measurement traits:		
Interval from calving to 1° luteal activity	Continuous (days)	Interval from calving to first luteal activity (2 subsequent measures of progesterone => 3ng/mL)
Average progesterone level	Continuous (ng/mL)	Expressed in ng/mL (during breeding period)
Cycle length	Continuous (days)	Interovulatory period
Luteal phase length	Continuous (days)	Interluteal period
Number of cycle per lactation	Count [1,2…n]	Derived by luteal activity over time
Delayed ovulation I	Binary [0/1]	The occurrence of a delay for >

		45d postpartum
Delayed ovulation II	Binary [0/1]	The occurrence of a delay for > 12d between 2 luteal phases
Delayed luteolysis I	Binary [0/1]	Delayed luteolysis during the first cycle with a persistent corpus luteum
Delayed luteolysis II	Binary [0/1]	Delayed luteolysis during subsequent cycles with a persistent corpus luteum
Incidence of silent heats	Binary [0/1]	Combining on-farm-recorded data and progesterone profiles
Days from first heat to first service	Continuous (days)	Combining on-farm-recorded data and progesterone profiles

Another issue concerning genetic aspects of fertility is that variance components might vary across parities. Several authors have reported heritability values estimated across lactations [12], [47], while other studies [45] reported different variance component estimates in the different parities and genetic correlations within the same trait measured on different lactation that were less than unity.

Heritabilities and correlations with other traits: For the reasons explained in the previous section many fertility traits are difficult to handle in parameter estimation and genetic evaluation. Most of the traits are analyzed either through linear or threshold models, although applications of survival analyses are not uncommon [48]. Models employed range from single sire models [49], to random regression animal models [50], single or multiple trait models [51] and with or without the specific modeling of censored data [49]. Whereas model complexity has increased exponentially over the last few years, heritability estimates for fertility remain relatively low, on average below 5%, mainly due to the large influence of management and environmental effects [5], which are not trivial to disentangle when evaluating fertility. A further aspect of heritability of fertility traits is represented by the limitedness of the conventional-recording fertility traits. When we move from conventional traits (e.g. days to first service) to other measures of fertility (e.g. days to first heat) the impact of genetic variance is much higher. Pryce [30] reported an heritability of 0.06 for the days to first service and 0.18 for the days to first heat. The difference between those 2 kind of traits derives by the interaction of other biological traits (e.g. the intensity at first estrous) and farmer decisions (e.g. voluntary waiting period) which can't be extrapolated from conventional recording. Thus, the heritability of fertility is rather higher if we shift to traits which are more representative of the cow physiology. But a national evaluation of fertility has to be based on large scale recording system, and the most of farmer-recorder data might be not reliable. In spite of low heritabilities though the phenotypic variation for most fertility traits is relatively large and provides a favorable opportunity for selection [52]. In the United States, DPR evaluations are available since 2003 and are currently calculated through an all breed animal model [53]. Heritability of DPR is currently estimated at approximately 4%. A summary of estimates of heritability of fertility traits as estimated by different authors is reported in table 2.

A summary of estimates of correlations between fertility traits and milk yield as estimated by different authors is reported in table 3. Correlations between fertility and production traits are generally negative [54], [55], [56], [57], [10], with values ranging between approximately 0.2 and 0.4 and increasing with the number of lactation as a consequence of the increased energy requirements with increased productions.

Table 2. Point estimates of heritability for different traits as reported by different authors

Author	**Year**	**h^2**	**Trait**	**Structure**
Abdallah and McDaniel.	2000	0.03	Calving to conception	Linear
Hou et al.	1981	0.01-0.21	Calving to first service	Survival
		0.008-0.12	Calving to Conception	Survival
Chang et al.	2004	0.03	Inseminations to Conception	Threshold
		0.04	Calving to conception	Linear
Pryce et al.	2001	0.001	Conception at first service	Linear
		0.18	Days to first observed heat	Linear
		0.06	Days to first service	Linear
Hodel et al.	1995	0.01-0.02	Non return rate 90 days	Linear
		0.02-0.03	Non return rate 90 days	Threshold
Veerkamp et al.	2001	0.07	Days to first service	Linear
		0.03	Calving Interval	Linear
Berry et al.	2003	0.02	Number of Inseminations	Linear
Muir et al.	2004	0.029	Non return rate 56 days	Threshold
González-Recio et al.	2006	0.04	Number of inseminations	Threshold
Wall et al.	2003	0.02	Number of inseminations	Linear
VanRaden et al.	2004	0.04	Pregnancy rate	Linear
Sewalem et al.	2010	0.017	Non return rate 56 days	Linear
		0.08	Calving to first service	Linear
		0.049	Calving to conception	Linear
Jamrozik et al.	2005	0.04	Non return rate 56 days	Linear
		0.09	Calving to first service	Linear
		0.07	Calving to conception	Linear
De Haas et al.	2007	0.08	Days to first insemination	Linear
		0.08	Days from first to last insemination	Linear
		0.04	Calving interval	Linear
		0.01	Number of services per conception	Linear
		0.01	Conception rate to first insemination	Linear
Schneider et al.	2005	0.037-0.056	Hazard of pregnancy	Survival
		0.04	Calving interval	Linear

Table 3. Estimated correlations between different traits and milk yield as reported by different authors.

Author	Year	R_g point estimate	Fertility trait	Production trait
Berger et al.	1981	0.47	Calving to conception	60-d Milk yield
		0.44	Number of inseminations	60-d Milk yield
		0.62	Calving to conception	305-d Milk yield
		0.62	Number of inseminations	305-d Milk yield
Hoekstra et al.	1994	−0.26	Non return rate 56 days	305-d Milk yield
Pryce et al.	1997	−0.19	Conception rate at first service	305-d Milk yield
Dematawewa and Berger	1998	0.55	Calving to conception	305-d Milk yield
		0.53	Number of inseminations	305-d Milk yield
Kadarmideen et al.	2000	0.41	Number of inseminations	305-d Milk yield
		−0.42	Conception rate	305-d Milk yield
Veerkamp et al.	2001	0.48	Number of inseminations	305-d Milk yield
		−0.49	Conception rate at first service	305-d Milk yield
Berry et al.	2003	Negative except in early lactation	Pregnancy rate	Test-day Milk yield
Muir et al.	2004	0.02	Non return rate 56 days	305-d Milk yield
González-Recio et al.	2006	0.63	Calving to conception	305-d Milk yield
		0.23	Number of inseminations	305-d Milk yield

Muir et al. [51] reported genetic correlations among different fertility traits for first lactation Holsteins. In their work, estimated genetic correlation for age at first insemination as heifer and 56 days non return rate as heifer was positive and small (0.08) while genetic correlation between age at first insemination as heifer and 56 days non return rate as cow was negative (−0.20). Non return rate as a heifer and as a first lactation cow were poorly related between themselves (0.22) but unrelated to calving interval. Higher, albeit small, correlations between reproductive performance traits were reported by other authors [58], [32].

De Haas et al., [59] reported correlations between fertility traits and body condition score. Correlation of days to first service with BCS was -0.42, while values of -0.62, -0.53 -0.27 and 0.60 were reported between BCS and days between first and last insemination, calving interval, number of services per conception, and conception rate at first insemination, respectively. Similar results were found by other authors [60], [61] .

Heringstad et al. [62], reported genetic correlations between disease occurrences and fertility traits. Correlation between number of clinical mastitis and services to conception (with censoring) were estimated to be 0.21. Furthermore, estimated correlations of 0.15, 0.07, 0.20, -0.34, 0.13, 0.18 were reported by the same author [63] between clinical mastitis and calving to first insemination interval, clinical mastitis and non return rate at 56 days, between ketosis and calving to first insemination, ketosis and non return rate at 56 days, and between retained placenta and calving to first insemination, and retained placenta and non return rate at 56 days, respectively.

Conclusion

Reproductive performance is a major determinant of farmers' profitability in dairy. Inadequate reproductive performance increases involuntary culling, reduces overall production and lowers calves per cow in a year increasing production costs and ultimately decreasing the farmer's profit. The antagonistic relationship between fertility and production traits is the main cause of the unfavorable trends for fertility when reproductive efficiency parameters are not included in selection programs. Furthermore, even if included in the breeding objective there is still a risk of deterioration of fertility due to low heritability if the emphasis placed on fertility is too little [5]. In spite of its importance fertility presents several challenges. Reproductive efficiency includes different physiological aspects; it's not easily defined, and suffers in some case of lack of reliable information. Reproduction is an economically relevant component of many livestock species. Beef cattle are no exception. Genetic improvement programs for fertility in beef have been hindered by the difficulty of developing reliable systems of data collection for fertility related events. An increasing body of knowledge of fertility in beef cattle is available (see [64] for a review). In addition the experience gained over the last decade by the dairy industry in selecting for increased fertility will represent a potential source of information for the implementation of efficient fertility selection programs in beef cattle. Nonetheless, the incorporation of these traits in beef genetic improvement programs will depend on the identification of suitable field recorded traits, and the consistent compilation of the information collected by the breed associations for its subsequent use [64].

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