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The genetic relationship between reproduction traits and milk urea concentration

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The aim of this research was to investigate the genetic relationship between reproduction traits and milk urea concentration (MU) during the first lactation of Polish Holstein-Friesian cows. The following reproduction traits were considered: interval from calving to first insemination, interval from first to last insemination, interval from calving to conception, number of inseminations to conception, first insemination conception rate and first insemination non-return rate to the 56th day. Data consisted of more than 1.2 million test-day records from 148,700 primiparous cows, for which fertility traits were available. Daily genetic correlations between MU and fertility traits were estimated with a random regression animal model. The Bayesian Gibbs sampling method was used to estimate the (co)variance components. Heritability of reproduction traits was low and ranged between 0.01 and 0.06. Heritability for MU was higher and relatively constant throughout the lactation (0.16-0.19). The genetic correlation between reproduction traits and MU in mid-lactation was close to zero, which suggests that MU measured close to the first insemination is of limited use in the indirect selection for fertility. Moderate genetic correlations between MU and reproduction traits, which were observed in the first two months of lactation, are sufficient for genetic improvement of fertility. However, better fertility was genetically related with higher MU, and an increase of MU concentration is undesirable.

KEY WORDS: air temperature / cow fertility / genetic correlation / milk urea

Effectiveness of cows' reproduction affects profitability of dairy farms. Deterioration in fertility decreases lifetime production, lowers the number of available replacement heifers and reduces the intensity of selection [Gonzalez-Recio *et al.*

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2004], but most of all, it is the cause of involuntary culling. Therefore fertility related traits were included in breeding goals in many countries. However, the relatively low heritability of fertility traits [see Tiezzi and Maltecca 2011 for a review] limits the reliability of genetic evaluations of reproduction traits [de Jong 2005, Sun *et al*. 2010]. An increased accuracy of estimated breeding values and genetic response in the case of fertility could be the result of the additional use of predictor traits in multiple-trait models. Some authors proposed the use of the body condition score (BCS) as an indicator trait for fertility [Berry *et al*. 2003], while others suggested milk fatty acids [Bastin *et al*. 2012], fat to protein ratio [Negussie *et al*. 2013] or milk urea nitrogen (MUN) [König *et al*. 2008]. The BCS and milk fatty acids are not routinely measured in Poland, which limits their use in indirect selection. However, milk urea concentration (MU) has been recorded since 2001. In many studies lower conception rates were observed in cows with a higher MUN concentration [Butler *et al*. 1996, Rajala-Schultz *et al*. 2001, Hojman *et al*. 2004, Arunvipas *et al*. 2007, Chaveiro *et al*. 2011]. Melendez *et al*. [2000] found an interaction between MUN and breeding season. They suggested that the effects of MUN might overlap with the negative effects of heat stress. On the other hand, Fatehi *et al*. [2012] hypothesized that a higher MU observed in the summer might be a reason for lower reproductive performance. In our previous study we found that MU increased along with the ambient temperature also in the winter months [Rzewuska and Strabel 2013a]. It is possible that a higher MU causes poor fertility, but also those traits might have the same source of variability and changes in both could be a consequence of the increased ambient temperature.

MU is a highly variable trait with the range of heritability that suggests its potential applicability in the genetic evaluation of Polish Holstein-Friesian cows [Rzewuska and Strabel 2013b]. The use of MU as a predictor trait requires the existence of genetic correlations between MU and reproduction traits. Due to the fact that the air temperature affected both traits of interest (MU and some reproduction traits), it should be eliminated when a genetic correlation between them is estimated. Hence, the aim of this study was to estimate genetic parameters of both the test-day MU recorded throughout lactation and reproduction traits for primiparous Polish Holstein-Friesian cows, taking into account the impact of climate factors.

Material and methods

The data was obtained from primiparous Polish Holstein-Friesian cows, which calved between 2001 and 2008. The data set contained 358,049 cows, for which complete reproduction and lactation information was available. The following fertility traits were defined on the basis of the available data: 1) continuous traits (in days): interval from calving to first insemination (**CF**), interval from first to last insemination (service period, **SP**), interval from calving to conception (days open, **DO**), 2) categorical trait: number of inseminations for conception (**NI**), 3) binary traits: first insemination conception rate (**FICR**) and first insemination non-return rate to the 56th day (**NR56**). The FICR was coded as 1 when the date of the first insemination was the date of conception, otherwise it was coded as 0. The NR56 was coded as 1 when a subsequent insemination was reported within 56 days (reinsemination during the same heat was not taken into account). Two classes of age at calving were defined, the threshold value between them was 24 months. Only records of the cows which were the progeny of sires with at least 20 daughters were included into the final data set. At least 10 observations in each class of herd-year of calving were required. After that restriction, the data set contained data from 148,700 primiparous cows, which were daughters of 2,915 sires and which calved in 5,990 herd-year classes.

Urea concentration in milk (MU) was measured in accredited milk quality laboratories by means of infrared spectrometry using a Combifoss (Milkoscan). Test-day observations with extreme values for MU were removed, the threshold of 0.5% extreme values was applied. Only test-day records measured between 5 and 305 days in milk (DIM) remained in the data set. Depending on how often milk samples were collected - once a month or once in two months, lactations without the minimum of 5 or 4 test-day records, respectively, were excluded. Only test-day records from cows, which were included in the data set containing information about reproduction traits, were considered in the analysis (1,243,970 records). Due to the interaction between the calendar month, in which milk samples were collected and the average ambient temperature in that month, which had been observed for MU in our previous study [Rzewuska and Strabel 2013a], month-temperature classes were created, after dividing temperature into 11 classes with 3-degree intervals, starting from -8.1°C. For each herd daily temperatures were obtained from the nearest of the 36 weather stations belonging to the Institute of Meteorology and Water Management and located throughout the country.

Estimation of (Co)Variance Components

The models applied are listed below in a simplified scalar notation for particular traits. Genetic correlations between the MU and the reproduction traits were estimated from the bivariate analyses.

The model for MU was as follows:

$$y_{ijklmn} = HTD_i + HY_j + AGE_k + b_M M_l + L_{1\text{-}4}(DIM)MT_m + L_{1\text{-}3}(DIM)AG_n + L_{1\text{-}3}(DIM)PE_n + E_{ijklmn}$$

where:

y_{ijklmn} – test-day observation of MU;

HTD_i – random herd-test-day effect;

HY_j – fixed effect of herd by year of calving;

AGE_k – fixed effect of age at calving;

b_M – linear regression coefficient of MU on test-day milk yield (M_l);

MT_m – fixed effect of the month-temperature class;

AG_n – random regression coefficients specific to animal additive genetic effect;

PE_n – random regression coefficients specific to permanent environmental effect;

$L_{1\text{-}4}(DIM)$, $L_{1\text{-}3}(DIM)$ – Legendre polynomials for DIM with 4 (for MT) or 3 (for AG and PE) parameters;

E_{ijklmn} – random residual error

The model for FICR was:

$$y = HY + MY + AGE + L_{1\text{-}4}(DIM) + b_M MM + AG + E$$

The model for CF and DO was:

$$y = HY + MY + AGE + b_{TC}TC + b_M MM + AG + E$$

The model for SP was:

$$y = HY + MY + AGE + b_{Tl}Tl + b_M MM + AG + E$$

The model for Ni was:

$$y = HY + MY + AGE + b_M MM + AG + E$$

The model for NR56 was:

$$y = HY + MY + AGE + E$$

In the models:

y – denoted a particular reproduction trait;

HY – fixed effect of herd by year of calving;

MY – fixed effect of month by year of the first insemination;

AGE – fixed effect of age at calving;

$L_{1\text{-}4}(DIM)$ – Legendre polynomials for DIM with 4 parameters;

TC – average temperature in month of calving;

TI – average temperature in month of the first insemination;

MM – the maximum test-day milk yield in lactation;

b_{MM}, b_{TC}, b_{TI} – linear regression coefficients of MM, TC and TI, respectively;

AG – random animal additive genetic effect;

E – random residual error.

In matrix notation the bivariate model may be written as:

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Uq} + \mathbf{Za} + \mathbf{Wp} + \mathbf{e}$$

where:

y – vector of observations;
q – vector of random HTD effects for MU;
b – vector of all fixed effects;
a – vector of random additive genetic effects;
p – vector of random PE effects for MU;
e – vector of residuals;
X, U, Z, W – respective incidence matrices.

The variance-covariance structure of the random effects for the bivariate models was defined as:

$$V\begin{bmatrix} q_1 \\ a_1 \\ a_2 \\ pe_1 \\ e_1 \\ e_2 \end{bmatrix} = \begin{bmatrix} I\sigma_{h1}^2 & 0 & 0 & 0 & 0 & 0 \\ & A\otimes G_1 & A\otimes G_{12} & 0 & 0 & 0 \\ & & A\otimes G_2 & 0 & 0 & 0 \\ & & & I\otimes P_1 & 0 & 0 \\ & & & & I\sigma_{e1}^2 & I\sigma_{e12}^2 \\ symm & & & & & I\sigma_{e2}^2 \end{bmatrix}$$

$$V\begin{bmatrix} q_1 \\ a_1 \\ a_2 \\ pe_1 \\ e_1 \\ e_2 \end{bmatrix} = \begin{bmatrix} I\delta_{h1}^{\ 2} & 0 & 0 & 0 & 0 & 0 \\ & A\otimes G_1 & A\otimes G_{12} & 0 & 0 & 0 \\ & & A\otimes G_2 & 0 & 0 & 0 \\ & & & I\otimes P_1 & 0 & 0 \\ & & & & I\delta_{e1}^{\ 2} & I\delta_{e12} \\ symm & & & & & I\delta_{e2}^{\ 2} \end{bmatrix}$$

where indices indicate the traits (1 - MU and 2 - one of the reproduction traits), σ_{h1}^2 is the variance of the random HTD effect, is the identity matrix, **A** is the matrix of the additive genetic relationship among animals, ⊗ is the Kronecker product, $\mathbf{G_1}$ is the covariance matrix of random regression coefficients for the additive genetic effect, $\mathbf{G_{12}}$ is the vector of covariances between random regression additive genetic coefficients and the additive genetic effect for the reproduction trait, and $\mathbf{G_2}$ contains only one value - the additive genetic variance of the reproduction trait, $\mathbf{P_1}$ is the covariance matrix of random regression coefficient for the permanent environmental effect, σ_{e1}, σ_{e1} and σ_{e12} are (co)variances of the random residual effects.

The linear model was applied to estimate variance components for all traits, including those of a binary nature. Although the linear model assumes the normality of traits, many studies have shown its potential applicability in the genetic evaluation of fertility traits [Jamrozik *et al*. 2005, Hossein-Zadeh and Ardalan 2010, Mucha and Strandberg 2011]. For categorical traits the application of the threshold model is theoretically more appropriate, but it is also associated with many limitations, such as problems with subclasses containing only one category of a binary trait, restriction to the use of sire models and large computational demand [Kadarmideen *et al*. 2000, Weigel and Rekaya 2000]. The heritability estimated by Kadarmideen *et al*. [2000] with the threshold model was slightly higher than the one estimated with the linear model; however, those authors noticed that the accuracy of selection might be lower with threshold models. Weller and Ron [1992] obtained a high correlation between solutions estimated for random effects both with linear and threshold models, applied to the same data set. Furthermore, the differences between rankings of animals obtained with the logit and the linear models decrease with an increase in the size of the dataset [Sun and Su 2010]. Thus, the animal model rather than the sire model should be applied [de Jong 2005]. It should also be noted that for a routine genetic evaluation of fertility traits in Poland the multitrait animal model was used. In view of all the above arguments the linear-linear animal model was chosen for bivariate analyses of the genetic relationship between MU and reproduction traits.

The Gibbs sampling algorithm was implemented to estimate the covariance components and regression coefficients [Misztal *et al*. 2002]. Marginal posterior distributions of each random effect were obtained from 100,000 samples, after discarding the first 20,000 samples as the burn-in period. Uniform priors were assumed for fixed effects and (co)variance components and normal distributions for random effects. The resulting conditional distributions were either multivariate normal for position parameters, or inverted Wishart for (co)variance components. The convergence of the Gibbs chains was monitored by inspecting plots of estimated variances.

Results and discussion

Heritability

The average MU for primiparous cows was 218.3 mg/l (92.2). Table 1 shows descriptive statistics for fertility traits. The heritabilities estimated for all the examined reproduction traits were low (max. 0.06, Tab. 1) and within the range reported in previous studies for Holsteins: from 0.02 to 0.03 for FICR, from 0.01 to 0.03 for NR56, from 0.02 to 0.05 for NI, from 0.01 to 0.09 for SP, from 0.03 to 0.09 for CF and from 0.02 to 0.08 for DO [e.g. Kadarmiden et al. 2003, Jagusiak 2005a,b, König *et al*. 2008, Hossein-Zadeh and Ardalan 2010, Sewalem *et al*. 2010, Sun *et al*. 2010,

Table 1. Descriptive statistics, distribution of records (binomial traits) and heritability estimates for the fertility traits (standard deviations in parentheses)

Traits[1]	Mean (SD)	Model	Median	Minimum	Maximum	Heritability (SD)
CF (days)	79.9 (26.1)	63	76	31	150	0.055 (0.005)
SP (days)	44.5 (56.2)	0	23	0	270	0.034 (0.003)
DO (days)	124.4 (59.9)	72	110	31	305	0.049 (0.004)
NI	2.10 (1.36)	1	2	1	12	0.029 (0.003)
	trait value			0	1	
FICR	number of observations			82493	66207	0.016 (0.002)
NR56				61450	87250	0.012 (0.002)

[1] CF – interval from calving to first insemination; SP – interval from first to last insemination; DO – interval from calving to conception; NI – number of inseminations to conception; FICR – first insemination conception rate; NR56 – first insemination non-return rate to day 56.

Ghiasi *et al.* 2011, Mucha and Strandberg 2011]. Many researchers have mentioned the fact that low heritability of fertility traits is a result of the problems with collecting large amounts of relevant phenotypes, the application of linear models and a large number of factors affecting reproduction. Not only cow physiology has a significant impact, but also reproductive management, accuracy in heat detection, appropriate nutrition and the experience of an AI technician. The AI technician might affect the traits describing the ability to conceive, but due to the lack of information we could not include this factor in the model.

The highest heritability was recorded for CF, which describes a cow's ability to recycle. A similar heritability was observed for DO. Among the traits describing a cow's ability to become pregnant, the binary traits had the lowest heritability (NR56 and FICR). As expected, similarly to the results reported in literature, the interval traits had a larger heritability than binary traits [Jagusiak 2005a,b, Jamrozik *et al.* 2005, Ghiasi *et al.* 2011]. In the current study the highest heritability was observed for CF. This trait is influenced by the farmer's decisions about the length of voluntary waiting period, the efficiency of estrus detection and the application of synchronization products, but it is the only trait independent of the effectiveness of insemination and pregnancy diagnosis. A similar heritability of CF and DO may have been caused by the fact that both traits were measured from the day of calving and the length of DO depended on the length of CF. The lowest heritability was found for NR56. The result for this trait was consistent with the findings published in literature, with heritability below 0.02, also for the Polish Black-and-White cattle [Jagusiak 2005a]. NR56 is included in fertility indices in many countries, including Poland. Gonzalez-Recio *et al.* [2006] suggested that NI is a better measure of female fertility. The heritability of this trait is higher than that of NR56, but NI might depend on DIM when the first insemination occurs. Although NI is accepted by farmers who use it to assess herd fertility, the information about that trait is available later than about CF and NR56 due to the length of the service period.

The daily heritabilities of MU, estimated with each of the bivariate models, were similar and on average they amounted to 0.16 (SD=0.007), which was within the range reported in literature, i.e. from 0.13 to 0.22 [Mitchell *et al*. 2005, König *et al.* 2008, Hossein-Zadeh and Ardalan 2010, Mucha and Strandberg 2011]. Some researchers found higher estimates for Canadian Holsteins [Wood *et al*. 2003, Miglior *et al.* 2007]. The results estimated in the current study were also lower than those estimated in the previous study for the same population (0.22) [Rzewuska and Strabel 2013b]. This may have been caused by the fact that the previous study took into account only cows from large herds and the number of animals included in the analysis was much lower. It could also have been the cause of greater changes in the heritability of test-day MU during lactation than that recorded in this study, in which daily heritability values were relatively constant throughout lactation, with slightly higher values at both ends of lactation (Fig. 1). In other studies, a U-shaped curve of MUN heritability was found. It is possible that a large number of observations used in the current study prevented higher estimates at the beginning and at the end of lactation, which are often shown to be artifacts of fitting the polynomials [Misztal *et al.* 2000]. The additive variability of MU is sufficient to use that trait in a genetic evaluation for Polish Holstein-Friesian cows. Heritability of MU was higher than heritability of fertility traits and their estimates were stable across the lactation, which suggests that MU is not only an easily measurable trait, but it also meets the other criterion determined for an indicator trait.

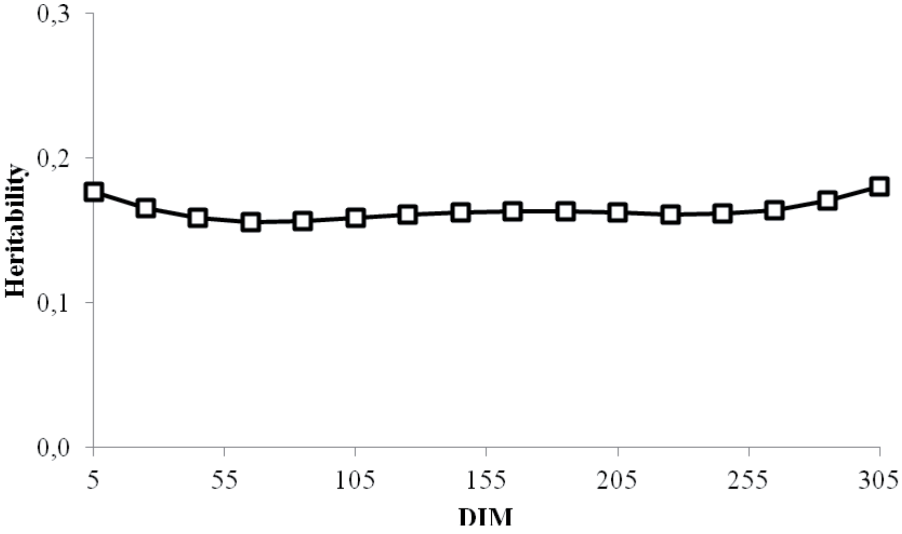

Fig. 1. Heritabilities of MU throughout the first lactation of Polish Holstein-Friesian cows, estimated with the bivariate model with FICR.

Genetic correlations

In order to determine the potential applicability of MU genetic evaluation in indirect fertility improvement, the knowledge of genetic correlations between MU and reproduction traits is of primary importance. Genetic correlations between MU and CF were weak (from -0.06 to 0.14), but relatively constant during lactation, with the lowest values at both ends of lactation and the highest in mid-lactation. The genetic correlation between MU and SP, DO and NI followed the same trend during lactation: negative at the beginning of lactation, close to zero during the period when the first insemination was administered, and positive during the last two months of lactation (Fig. 2). The curves for genetic correlations of MU with FICR and with NR56 had a mirror pattern. Having considered most of the reproduction traits (DO, SP, FICR, NR56), we could conclude that a higher MU at the beginning of lactation was genetically related to better fertility. Therefore, an increase in MU in the first month of lactation (when the lowest concentration was observed) due to the selection could indirectly improve the reproduction traits observed at later stages of lactation. However, a favorable relation between the fertility traits and MU in the first month of lactation, recorded in our research, was not confirmed in other studies. Mucha and Strandberg [2011] observed a favorable genetic association between MUN and fertility, although especially at later stages of parity, whereas an antagonistic association was estimated in this study. Differences in the relationship pattern throughout lactation may have been caused by the relatively low and constant concentration of MUN

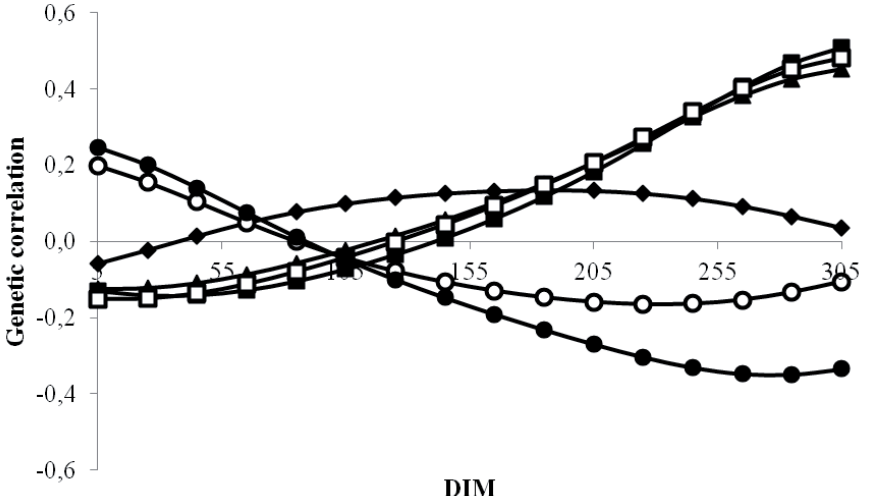

Fig. 2. Genetic correlations between milk urea concentration (MU) and CF (♦), SP (■), DO (▲) NI (□), NR56 (○), FICR (●) for different days in milk (DIM) in the first lactation of Polish Holstein-Friesian cows. CF – interval from calving to first insemination; SP – interval from first to last insemination; DO – interval from calving to conception; NI – number of inseminations to conception; FICR – first insemination conception rate; NR56 – first insemination non-return rate to day 56.

during lactation in Swedish Holstein cows. This may have also resulted from the higher average daily milk production than in Polish Holsteins (27.5 vs. 20.3). As it was shown in this study, the milk yield affects both MU and fertility traits, therefore it might be one of the factors causing differences in the results. It may also be suspected that there are differences in the genetic correlation between populations. The change in the direction of the relationship between MU and reproductive traits throughout lactation, found in the current study, is in concordance with a low genetic correlation between MU values measured on distant DIM (it decreased to 0.37, Fig. 3). We could conclude that MU had a different genetic background at the beginning and at the end of lactation, therefore the genetic correlation between MU and fertility changes at different stages of lactation.

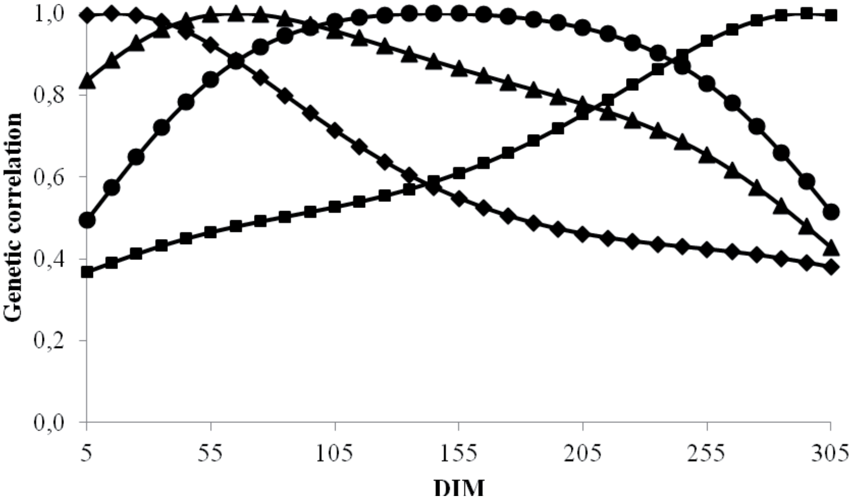

Fig. 3. Genetic correlations between a given DIM and the rest of lactation for milk urea concentration (MU) in the first lactation (♦ 15, ▲ 65, ●145, ■ 295 DIM).

Regardless of the favorable genetic relationship between MU and DO, SP, FICR and NR56 at the beginning of lactation, the genetic correlation between MU and CF in the same period was close to zero. It indicates that MU concentration observed in the first two months of lactation was correlated with cows' ability to conceive rather than with their ability to recycle. That result was contradictory to the estimates made by König *et al*. [2008], where the value of the correlation between the CF and the level of MUN was 0.29. MUN was defined as the mean of the first two test days in lactation. In the current study the highest genetic correlation between CF and MU was observed in the fifth month of lactation, but still it remained relatively low. Genetic correlations between other reproduction traits and MU, measured in the same period when the first insemination usually was administered, were also close to zero. This is in agreement with the findings by Mitchell et al. [2005], who analyzed MUN measured within ±30 days of the first service, on average administered on 85.8 DIM. These results indicate that the applicability of MU from mid-lactation as an indicator trait for fertility is limited.

The genetic correlation between MU measured at later stages of lactation and FICR and NR56 indicates that some genes may affect fertility, while simultaneously underlying the urea synthesis at the final stages of lactation. It is difficult to identify the physiological pathways that connect these two traits. However, it is possible that adaptation of an organism to pregnancy and changes in the cow's metabolism occur at the same time. On the other hand, cows with poor fertility may be genetically predisposed to high production of MU at later stages of lactation. It should be highlighted that in the final part of lactation only such traits as DO, SP and NI are observed and it is only in cows, which did not get pregnant at earlier stages of lactation. Nevertheless, even for those traits the beginning of lactation is crucial and breeders should focus on it. Therefore, genetic correlations between fertility traits and MU found in the first two months of lactation are particularly important. The direction of those correlations would cause the undesirable increase of MU concentration in milk, connected with genetic improvement of fertility.

Applicability of MU to support selection for fertility traits is limited due to: 1) the very low genetic correlation between reproduction traits and MU measured close to the time of the first insemination; 2) moderate, but unfavorable genetic correlations between MU and reproduction traits in the first two months of lactation.

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