

## Genetic Parameters for Cystic Ovarian Disease in Dutch Black and White Dairy Cattle

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### ABSTRACT

Cystic ovarian disease (COD) is one of the most frequently diagnosed gynecological findings in dairy cattle. It causes temporary infertility and is likely to affect reproduction as well as production parameters in cows. The objectives of this study were to investigate the heritability of COD in a Dutch Black and White population and to estimate the genetic and phenotypic relationships with milk production traits. In the data set used, the overall incidence of COD was 7.7% (1204 COD diagnoses in 15,562 lactations). The farm incidence varied between 1.9 and 11.3%. The estimated heritabilities on the underlying and observable scales were 0.102 and 0.087, respectively. The genetic correlations between COD and 305-d milk, fat, and protein yields were 0.345, 0.379, and 0.441, respectively. We concluded that a genetic predisposition for COD exists in Dutch Black and White dairy cattle. The genetic correlations between COD and yield traits indicate that ongoing selection for production will increase the incidence of COD.

**(Key words:** cystic ovarian disease, dairy cattle, genetic parameters)

**Abbreviation key:** COD = cystic ovarian disease; VAMPP = Veterinary Automated Management and Production Program.

### INTRODUCTION

Cystic ovarian disease (COD) is one of the most frequently diagnosed gynecological findings in dairy cattle. In dairy cattle, COD is the presence of a large follicular structure (>2.5 cm) on one or both ovaries in the absence of a corpus luteum (Roberts, 1986). Clinically, COD is most frequently (62 to 85%) characterized by anestrus (Day, 1991) because of the production of progesterone

by more or less luteinized cysts. However, nymphomania and irregular cycles are also common (Kasari et al., 1996). COD causes temporary infertility and is likely to affect reproduction as well as production parameters in cows. The COD is mostly associated with a higher 305-d milk yield (Erb et al., 1985), increased number of days open, increased number of inseminations per conception, and increased culling (Gröhn et al., 1990).

The primary cause of ovarian cyst development has not been clearly established because of the variety of histological characteristics, various abnormal hormonal patterns, and differing therapeutic responses. Currently, the most widely accepted hypothesis is that COD results from a neuroendocrine imbalance involving the hypothalamic-hypophyseal-gonadal axis (De Silva and Reeves, 1988; Eyestone and Ax, 1984; Kesler and Garverick, 1982; Lopez-Diaz and Bosu, 1992). One of the possible causes of this imbalance is an insufficient feeding of the high-producing cow, resulting in ketosis (Gröhn et al., 1990). Energy deficit and low insulin concentrations may limit the responsiveness of the ovary to gonadotrophin stimulation (Butler and Smith, 1989; Opsomer et al., 1999).

The genetic background of COD has been investigated in a number of studies, and heritability estimates range from 0.00 to 0.13 (Dohoo et al., 1984; Lin et al., 1989; Solbu, 1984; Uribe et al., 1995). The wide range in estimates is caused by the generally small data sets used in the analyses. Furthermore, data collection protocols might vary between studies. Selection in dairy cattle is largely focused on milk production traits. Knowledge about the genetic correlations between these traits and COD is important for prediction of the correlated response in COD incidence with this selection strategy. An unfavorable correlation indicates that frequency of COD would increase with selection on milk production traits, unless attention is paid to COD or related reproductive parameters in selection.

The objectives of this study were to investigate the heritability of COD in Dutch Black and White dairy cattle and to estimate the genetic and phenotypic relationships with milk production traits.

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## MATERIALS AND METHODS

### Data

The veterinary practice Mid-Fryslân monitored fertility on 38 Holstein-Friesian dairy farms in Friesland (Northern Netherlands) according to a standard protocol (Hooijer et al., 1999). Fertility data were collected during routine visits carried out every 4 wk from 1987 to 1997. In short, the protocol consisted of rectal and vaginal examinations for COD of all cows 30 d or more postpartum, rectal examinations of cows without registration of estrus, examination of repeat breeders, and examination for pregnancy between 40 and 70 d after the last insemination. A cow was diagnosed as COD positive if follicular structures with a diameter >2.5 cm were found present on one or both ovaries without a palpable corpus luteum. Cows with diagnoses of COD were usually treated with GnRH. Also PGF<sub>2α</sub> or progesterone (ear implant or intravaginal device) was used. All treated cows were checked again during the next visit, unless they were inseminated in the meantime. All recordings on diagnosis, date, and treatment were entered into a veterinary automated management and production program (VAMMP; Noordhuizen and Buurman, 1984). The initial data set comprised 1508 lactations from 38 herds in which at least one treatment for COD was carried out. Most herds did not participate in the program for the entire period of the study: 8 herds participated 4 yr or less, whereas 20 farms participated 8 yr or more in the study. Only records of cows affected by COD were extracted from VAMPP. All farms participated in the national pedigree and milk-recording scheme. Registration and milk data from these cows were obtained from the national breeding organization (NRS), Arnhem, The Netherlands. Milk information of all other cows present in the herds during the corresponding period was added to the data set. The data included realized or extended 305-d productions of milk, fat, and protein. Extended production records concerned lactation records with a lactation length less than 305 d, or lactations in progress. Records with <60 d of lactation were not included.

Pedigree information for all cows was retrieved from the national pedigree records as maintained by the national breeding organization. Parents with unknown ancestors were classified into genetic groups according to the percentage of Holstein-Friesian blood combined with year of birth (five levels), sex of the parent, and sex of the animal. Classes with too few observations were joined with one of the two adjacent classes. This procedure resulted in 35 genetic groups.

Yearly incidences of COD in the first and last years could not be calculated, because in these years recording occurred only for a part of the year. Therefore, we decided to include only lactations that started after January 1,

1987, and lactations that ended before January 1, 1997. These restrictions led to exclusion of 1494 records. Combining the data sets and screening for inconsistencies resulted in a data set of 15,562 records from 38 herds, including 1204 records of COD-positive diagnoses.

### Statistical Analyses

**Genetic Variance.** The trait COD was considered as a binary expression (present/absent) of an underlying variable that is influenced by genetic and environmental factors. As soon as the underlying variable exceeded a certain threshold, the event (COD) was occurring. The genetic analysis was based on this threshold model, assuming an unobservable, continuously distributed variable underlying COD. Data were analyzed using the following animal model.

$$Y_{ijkl} = H_i + YS_j + L_k + A_l + P_l + e_{ijkl} \quad [1]$$

where  $Y_{ijkl}$  = value for COD of observation  $ijkl$ , but transformed to the underlying scale;  $H_i$  = fixed effect of herd  $i$ ;  $YS_j$  = fixed effect of year-season  $j$ ;  $L_k$  = fixed effect of lactation  $k$ ;  $A_l$  = random effect of animal  $l$ ;  $P_l$  = random permanent environmental effect of animal  $l$ ; and  $e_{ijkl}$  = random residual error associated with observation  $ijkl$ .

The herd effect comprised 38 classes, and the year-season effect comprised 48 classes. The fixed effect lactation number contained three classes, whereby lactations three and higher were grouped together in class: 3+. Fixed effects to be included in the model were determined by results from a preliminary least squares analysis (procedure GLM; SAS, 1989). The following fixed effects were considered in the preliminary analysis: herd, year, and season of calving together with their interactions and the effect of lactation number. Year-season rather than herd-year-season effect was used to avoid having many subclasses in which all observations were 0 or 1, which complicates estimation of variance components. We did not consider the use of random year-season effects as suggested by Harville and Mee (1984).

The genetic analysis was conducted using a REML approach as implemented in the software package AS-REML (Gilmour et al., 1998). In this approach the second derivative of the likelihood function is solved by an average information algorithm.

The analysis, according to the model, resulted in estimates for variance components due to animal ( $\sigma_a^2$ ), permanent environmental effect ( $\sigma_{pe}^2$ ), and residual error ( $\sigma_e^2$ ). The heritability in case of an underlying logistic distribution can be computed (Gilmour et al., 1998) as

$$h_u^2 = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_{pe}^2 + \sigma_e^2 \times 3.3} \quad [2]$$

in which the residual variance is multiplied by 3.3 to convert the value to that of a normal distribution.

The computed heritability on the underlying scale can be transformed (Cameron, 1997) to a value on the observable scale by

$$h_o^2 = \frac{z^2}{p(1-p)} * h_u^2 \quad [3]$$

where  $h_o^2$  = heritability on the observable scale;  $h_u^2$  = heritability on the underlying scale;  $p$  = incidence of the binary trait; and  $z$  = height of the normal distribution curve corresponding to incidence  $p$ .

**Genetic covariances.** The relationship of COD with milk production traits was investigated in a set of bivariate analyses. A bivariate analysis of binary and continuous traits, keeping the concept of an underlying trait (for the binary trait), is not possible in ASREML. Consequently, in the bivariate analysis COD was assumed to follow a normal distribution:

$$Y_{ijkl} = H_i + YS_j + L_k + P_1 + A_l + e_{ijkl} \quad [4]$$

$$Z_{ijklm} = H_i + YS_j + L_k + D_m + A_l + e_{ijklm} \quad [5]$$

where  $Y_{ijkl}$  = value for COD of observation  $ijkl$  (0 or 1);  $Z_{ijklm}$  = 305-d yield in kilograms of milk, fat, or protein production for observation  $ijklm$ ;  $H_i$  = fixed effect of herd  $i$ ;  $YS_j$  = fixed effect of year-season  $j$ ;  $L_k$  = fixed effect of lactation  $k$ ;  $D_m$  = fixed effect of days open-class  $m$ ;  $P_1$  = random permanent environmental effect of animal

$l \sim N(0, I\sigma_{pe}^2)$ ;  $A_l$  = random effect of animal  $l \sim N(0, A\sigma_a^2)$ ; and  $e_{ijkl(m)} =$  random error associated with observation  $ijkl(m) \sim N(0, I\sigma_e^2)$ .

For production traits, a fixed effect to account for the effect of days open was included, because we were interested in the relationship between COD and production at a constant number of days open. Days open was divided into 24 classes, by defining one class for cows with <45 d open and one for cows with >305 d open. For the period between these two extremes, 21 classes were defined (19 classes of 10 d and 2 classes of 30 and 40 d, respectively). Cows with an unknown number of days open were allocated to a separate class.

Only first lactation records for milk production traits were used for these analyses. The data structure did not allow fitting a permanent environmental covariance between lactation records and COD. Thus, in these analyses the permanent environmental effect was only considered for COD.

## RESULTS

The overall incidence of COD was 7.7% (1204 COD treatments from 15,562 lactations). The farm incidence was, on average, 7.2% and varied between 1.9 and 11.3%. The COD incidence showed a large increase over the 10 yr (Table 1). Overall COD incidence increased from 3.0% in 1987 to 9.5% in 1996. The estimated effects of years were derived as linear combinations from the year-season effects as estimated with the threshold model. The year-season effect had a significant influence on the incidence of COD ( $P < 0.001$ ). These solutions also showed an increase over the years of study. The predicted contrast

**Table 1.** Observed cystic ovarian disease incidence per year and estimated year effects<sup>1</sup> at the underlying and observed scales estimated from the genetic threshold model, as contrasts with year 1987.<sup>2</sup>

Year	Calvings (no.)	Incidence (%)	Estimated contrast	
			Underlying scale <sup>2</sup>	Observed scale (%) <sup>3</sup>
1987	460	3.04	—	—
1988	912	3.18	0.10 (0.41)	0.31
1989	1495	5.42	0.66 (0.38)	2.78
1990	1556	5.98	0.73 (0.37)	3.18
1991	1755	7.35	0.96 (0.37)	4.67
1992	1785	7.68	0.97 (0.37)	4.74
1993	1914	9.82	1.21 (0.37)	6.67
1994	1843	9.60	1.14 (0.37)	6.07
1995	1923	9.26	1.11 (0.38)	5.82
1996	1820	9.45	1.04 (0.38)	5.27
Total	15,562	7.74		

<sup>1</sup>Year effects were obtained as averages of the year-season classes within each year.

<sup>2</sup>Standard errors of contrasts are given in parentheses.

<sup>3</sup>The predicted difference in incidence (observed scale) is calculated from the contrast in the underlying scale as incidence =  $\{1/(1 + e^{-(-3.434 \cdot \text{contrast})})\} * 100\% - 3.04$  where  $-3.434$  corresponds to an incidence of 3.04%, i.e., the average incidence in 1987.

**Table 2.** Observed cystic ovarian disease incidence in first, second, and third and greater (3<sup>+</sup>) lactations and the estimated lactation number effect at the underlying<sup>1</sup> and observed scales estimated from the genetic threshold model, in contrast with lactation 1.

Lactation	# Calvings	Incidence (%)	Estimated contrast	
			Underlying scale <sup>2</sup>	Observed scale (%)
1	4379	5.89	—	—
2	3500	8.34	0.41 (0.09)	2.62
3 <sup>+</sup>	7683	8.51	0.54 (0.09)	3.58

<sup>1</sup>The predicted difference in incidence (observed scale) was calculated from the contrast at the underlying scale as incidence =  $\{1/(1 + e^{-(-2.831-\text{contrast})})\} * 100\% - 5.56$  where  $-2.831$  corresponds with an incidence of 5.56%, i.e., the predicted incidence in lactation 1.

<sup>2</sup>Standard errors of the estimated contrasts are given in parentheses.

between 1987 and 1996 was 1.04 with the underlying scale, which corresponded with a predicted increase of 5.3% in the incidence. Over years, season had no systematic effect on incidence of COD.

Table 2 shows that the observed incidence of COD was lowest in lactation 1 and highest in lactation 3<sup>+</sup>. The effect of lactation number was significant ( $P < 0.001$ ) and was mainly due to a large difference between first lactation and other lactations.

The estimates for the variance components from the analysis using equation [1] are shown in Table 3. The variance components correspond with heritability at the underlying scale of 0.102 ( $\pm 0.033$ ). The variance due to permanent environmental factors was considerably smaller than the additive genetic variance. By using the overall incidence of COD of 7.7% in equation [3], the heritability on the observable scale became 0.087. The average breeding values for COD of all cows per year of calving, based on the heritability on the underlying scale, are shown in Table 4. They increased from  $-0.01$  in 1987 to 0.20 in 1996, indicating a genetic trend in the population.

The unadjusted means of production and reproduction traits are given in Table 5 for each of the three lactation classes by COD status. It appeared that the average 305-d production of cows with COD is higher than in cows without COD. A longer lactation length accompanied this increase in 305-d production.

Estimates for additive genetic variance and heritability for production traits during first lactation and correlation estimates from the bivariate analyses of COD and

305-d milk production traits are given in Table 6. The heritability for milk production traits ranged from 0.26 for protein to 0.38 for milk. The genetic correlation with COD ranged from 0.34 for milk production to 0.44 for protein production. The environmental correlations were all very close to zero. The heritability for COD in these analyses was 0.03, which was considerably lower than the estimate from the univariate analysis (Table 3) in which a threshold model was applied. The lower estimate, however, was consistent with the result of a univariate linear model applied to first lactation data.

## DISCUSSION

Genetic analysis of COD requires a scheme for large-scale data collection as well as a uniform recording protocol. In this study, uniform collection was achieved by a single veterinary practice that worked with a standard recording protocol for all practitioners involved. The recording protocol involved monthly visits to all participating farms and gynecological examination of all cows at fixed points during lactation. The data set created was the result of a carefully designed and well-conducted field study (Hooijer et al., 1999). A total of 15,562 lactations was used in the present study. Until now, only the New York State College of Veterinary Medicine (Lin et al., 1989) had collected a data set of comparable size.

In this study a univariate threshold model was used to estimate the heritability of COD (Table 3). Use of this model resulted in heritability of 0.102 at the underlying scale, which corresponded with a heritability of 0.087 at the observed scale. Ashmawy et al. (1990), Chen et al. (1990), and Uribe et al. (1995) also estimated genetic parameters for COD by using the concept of an underlying trait, i.e., by using a nonlinear threshold model. Ashmawy et al. (1990) used a sire model and found a heritability of 0.15 ( $\pm 0.44$ ) for heifers and 0.11 ( $\pm 0.65$ ) for second lactation cows. Chen et al. (1990) found a heritability of 0.54, and Uribe et al. (1995) reported a heritabil-

**Table 3.** Heritability for cystic ovarian disease based on estimates of variance components ( $\sigma^2$ ) and SE with a threshold model.

Source	$\sigma^2$	SE ( $\sigma^2$ )	$h^2$	SE ( $h^2$ )
Animal	0.386	0.127	0.102	0.033
Permanent environment	0.111	0.122		
Residual	3.30			

**Table 4.** Average breeding values of cows per year of calving.

Year	EBV	SD
1987	-0.01	0.02
1988	0.01	0.02
1989	0.03	0.02
1990	0.06	0.02
1991	0.10	0.02
1992	0.14	0.02
1993	0.18	0.02
1994	0.18	0.02
1995	0.19	0.02
1996	0.20	0.02

ity of 0.13 for first lactation cows and 0.08 over all lactations. The heritability estimates of COD computed with a linear model were 0.12 (Lin et al., 1989), 0.07 (Uribe et al., 1995), -0.04 to 0.08 (Solbu, 1984), and 0 (Dohoo et al., 1984). The wide range in heritability estimates may reflect differences between populations. In most studies, however, the data sets and progeny group sizes were relatively small, which prevented accurate estimation of the heritability. In addition, one must realize that disease events are more accurately recorded if the herds are involved in a particular study with regular visits by veterinarians rather than in a continuous national health recording program (Mäntysaari et al., 1993).

In the present study, a linear model was used for estimating the relationship of COD with milk production traits, because it was not possible to apply a bivariate model with one discrete trait and one continuous trait. The analyses indicated that the increased incidence of COD was caused by environmental and genetic factors. The presence of positive genetic correlations of COD with milk production traits will cause an increase in COD incidence when selection is applied on the production traits. The impact of the magnitude of the estimated genetic correlations is explained as follows. The correlated response (CR) of COD to selection of a single record of milk yield can be computed as follows:

$$CR = i h_m r_g \sigma_{cod}$$

where  $i$  = selection intensity,  $h_m$  = square root of the heritability of milk,  $r_g$  = genetic correlation between milk with COD, and  $\sigma_{cod}$  = genetic standard deviation of COD. Based on the estimates in this study, selection for 305-d milk yield will increase the incidence of COD by 1.5% per 500-kg increase in milk yield.

Although genetic correlations between COD and milk production traits exist in this study, the literature provides variable results concerning the relationship between milk yield and COD. Laporte et al. (1994) reported that the observed milk production in the current lactation until the occurrence of COD is an important risk factor for COD. Erb et al. (1985) merely noticed a weak relationship between probability of cystic ovaries and milk yield in the previous lactation. Nanda et al. (1989) concluded that COD is not particularly a disease of higher yielding cows and that COD has no discernible effect on milk yield or its pattern. A possible explanation for the antagonistic relationship between COD and production is that cows in early lactation, which are trying to meet the increased requirements for milk production, are more susceptible to environmental changes with hormonal implications as result (Butler and Smith, 1989). Uribe et al. (1995) found a small, negative correlation between COD and milk production, indicating that selection for high volume of milk is not antagonistic or predisposing to the disease. Lyons et al. (1991) found no genetic correlation (-0.01) of ovarian cysts with milk production but a positive genetic correlation with fat (0.24). Mäntysaari et al. (1993) found genetic correlations between milk production and ovulatory disorders of 0.65 and 0.02 for Finnish cows during their first and second lactations, respectively.

Antagonistic correlations between milk yield and fertility traits in general indicate that selection for high milk yield leads to a reduction in fertility. However, if high-producing cows are given more opportunities to rebreed, or if breeding is delayed in high-producing cows, the negative association between production and fertility will be biased by management decisions (Bagnato and Oltenucu, 1993; Philipsson, 1981). By inclusion of num-

**Table 5.** Average 305-d productions, lactation lengths, and days open for cows without (0) and with (1) cystic ovarian disease (COD) in lactations 1, 2, and higher (3<sup>+</sup>).<sup>1</sup>

Trait	Lactation 1		Lactation 2		Lactation 3 <sup>+</sup>	
	COD = 0	COD = 1	COD = 0	COD = 1	COD = 0	COD = 1
Cows (no.)	4121	258	3208	292	7029	654
Milk production (kg)	6015	+465	7016	+548	7447	+389
Fat production (kg)	272	+21	317	+19	338	+21
Protein production (kg)	208	+16	246	+19	258	+13
Lactation length (days)	314	+53	305	+35	303	+29
Days open	125	+41	117	+36	113	+26

<sup>1</sup>Performance of cows with COD is expressed as deviation from cows without COD.

**Table 6.** Estimates for additive genetic variance and heritability for production traits during first lactation and correlation estimates from the bivariate analyses of cystic ovarian disease (COD) with 305-d milk production traits.

Trait	Production trait		Correlation with COD	
	$\sigma_g^2$	$h^2$	$r_g$	$r_e$
Milk (kg)	283,446 (34,274)	0.38 (0.04)	0.34 (0.11)	0.07 (0.02)
Fat (kg)	435 (62)	0.32 (0.04)	0.38 (0.12)	0.09 (0.02)
Protein (kg)	188 (30)	0.26 (0.04)	0.44 (0.12)	0.07 (0.02)

<sup>1</sup>SE are in parentheses.

ber of days open in the genetic model, this problem has been partly accounted for in this study.

## CONCLUSIONS

The heritability of COD as estimated in this study indicates a genetic predisposition for COD in Dutch Black and White dairy cattle. The genetic correlations between COD and 305-d milk production traits indicate that, without further measures, the incidence of COD will increase with ongoing genetic selection for milk production traits.

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