Relationships Between the Concentration of Insulin-Like Growth Factor-1 in Serum in Dairy Cows in Early Lactation and Reproductive Performance and Milk Yield

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ABSTRACT

The objective of this study was to evaluate the relationships of different insulin-like growth factor-1 (IGF1) measures [5 distinct IGF1 concentrations on particular days, area under the curve (AUC), and linear regression coefficient] in the postpartum period in lactating dairy cows and reproductive performance. A total of 417 healthy multiparous Holstein-Friesian cows were enrolled in the study. Serum samples for the determination of the concentration of IGF1 were collected on d 0, 4, 10, 20, and 40 postpartum (pp). The concentration of total IGF1 in serum was determined by immunometric chemiluminescence immunoassay. All cows were examined for vaginal discharge as a sign of clinical endometritis at 20 d pp by external inspection and rectal palpation. The mean concentration of IGF1 ranged from 57 ± 18.9 ng/mL within the first 12 h pp to 74 ± 19.9 ng/mL at 40 d pp. On d 10 pp, first and all artificial insemination conception rates were greater in cows with IGF1 concentrations above the median compared with cows with IGF1 concentrations below the median. Cows with greater AUC (second to fourth quartile) conceived earlier (11.4, 16.0, and 18.8 d) than cows in the first IGF1 quartile (117.0 ± 43.6). Proportion of cows pregnant within 200 d pp increased significantly from the first to the third IGF1 quartile of AUC (58.7, 66.7, and 74.0%). The proportion of cows culled decreased from the first to the fourth IGF1 quartile. Correlations between IGF1 measures and days to pregnancy were significant (except for the linear regression coefficients) but low ($R^2 = 0.0009$ to 0.025). Differences between single or composite measurements of IGF1 were not significant. We could also demonstrate a statistically significant correlation between the concentration of IGF1 in serum and the average 10-d milk production (31.6 to 44.0 kg). In conclusion, our study indicates that single or multiple measure-

ments of IGF1 concentration in the postpartum period have very limited value to predict individual fertility in dairy cows.

Key words: insulin-like growth factor, reproductive performance, milk yield

INTRODUCTION

Severe negative energy balance is associated with essential changes in the growth hormone (GH)-IGF axis such as downregulation of liver GH receptors and GH resistance of hepatic tissue (Andersen et al., 2004; Fenwick et al., 2008). Early lactation in dairy cattle is characterized by elevated blood concentrations of GH when concentrations of IGF1 in serum are low (Butler et al., 2003; Radcliff et al., 2006). Concentration of IGF1 (cIGF1) increases in the third week after calving when the liver GH receptors are upregulated and the hepatic tissue responds with an increased synthesis of IGF1 (Wathes et al., 2003). The concentration of IGF1 in plasma in dairy cows is influenced by parity (Kerr et al., 1991), stage of lactation (Wathes et al., 2007), photoperiod effects (Muthuramalingam et al., 2006), and stage of the ovarian cycle (Pushpakumara et al., 2003).

The reasons for poor reproductive performance in dairy cows are multifactorial. Transition cow management and nutrition have been recognized as the most important variables in reproductive performance (Drackley, 1999). Imbalanced nutrition during the dry and early postpartum (pp) period results in reduced concentrations of IGF1 and a low frequency of LH pulses, followed by delayed resumption of ovarian cyclicity. Concentrations of BHBA, NEFA, and triacylglycerol increase, whereas cIGF1 decreases (Jorritsma et al., 2003; Roche, 2006).

The plasma cIGF1 in the periparturient period and at the time of insemination has been described as a useful predictor for reproductive performance in dairy cattle. High cIGF1 in these periods had positive relationships to reproductive performance (Patton et al., 2007). Cows were less likely to conceive after first service

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when their plasma cIGF1 was <25 ng/mL in the first week after calving (Taylor et al., 2004). Cows with low cIGF1 postpartum had longer intervals from calving to resumption of cyclicity (Roberts et al., 1997; Beam and Butler, 1999). Furthermore, IGF1 has been demonstrated to influence ovarian functions such as follicular growth as well as maturation and the development of the embryo (Diskin et al., 2003; Thatcher et al., 2003). Concentration of IGF1 in plasma was also related to the recrudescence of corpus luteum activity (Thatcher et al., 1996). It is well documented that endometritis has a negative impact on reproductive performance (LeBlanc et al., 2002). Information on relationships between cIGF1 and the prevalence of endometritis, however, is not available.

The objectives of this study were 2-fold: 1) to evaluate the relationships between the concentration of IGF1 in serum and reproductive performance and milk yield in multiparous dairy cows and 2) to compare the diagnostic value of different IGF1 measures (i.e., 5 distinct IGF1 concentrations on particular days, area under the curve, and linear regression coefficient) for prediction of reproductive performance.

MATERIALS AND METHODS

All procedures in this trial were conducted according to the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) regulations relating to Good Clinical Practice and Clinical Trials (GCP). The study was conducted on a commercial dairy farm in Germany. A total of 1,300 Holstein cows were housed in free-stall barns with rubber mats and slotted floors. Cows were milked 3 times daily. Herd average milk yield was 10,300 kg per lactation with 3.97% fat and 3.37% protein. A total of 417 multiparous cows were enrolled in the study. The age of the cows ranged from 2 to 7 lactations, with 43.2% of the cows in second lactation.

Estrus detection was performed by an AI technician twice a day for approximately 60 min/d. Furthermore, the milkers observed the cows 3 times a day for signs of estrus. Pedometers were used to support estrus detection efficiency (De Laval, Glinde, Germany). A voluntary waiting period was set at 50 d pp. No timed breeding protocols (e.g., Ovsynch) were used.

A postpartum examination was conducted between 20 and 26 d pp by external inspection and rectal palpation to detect vaginal discharge as a sign for chronic endometritis. Cases of endometritis were classified depending on the amount of pus in the discharge (LeBlanc et al., 2002). Cows with vaginal discharge received 150 µg of Cloprostenol i.m. (PGF Veyx forte,

Veyx, Schwarzenborn, Germany). This treatment was repeated 14 d later.

Reproductive performance data were obtained from the herd management program (Herde, Agrosoft, Paretz, Germany). Milk yield from all individual milkings of the cows enrolled in the study was recorded for 305 d pp.

Blood Sampling Schedule and IGF1 Assay

Serum samples were collected within 12 h after calving (d 1) and on d 4, 10 (± 2 d), 20 (± 2 d), and 40 (± 2 d) pp. Blood sampling was performed at the same time every day—immediately after the morning milking—by puncture of the vena coccygea mediana. A vacutainer system (Venoject II, Terumo Europe N.V., Leuven, Belgium) was used. Samples were centrifuged (10 min, $1,000 \times g$), and serum was stored in 2 aliquots at -20°C until analysis.

The concentration of total IGF1 in serum was determined by an immunometric chemiluminescence immunoassay (Immulite 2000 IGF-I-Assay, Bad Nauheim, Germany). The intra- and interassay coefficients of variation were 7.7 and 3.0%, respectively.

Statistical Analysis

Data were analyzed using SPSS for Windows (Version 12.0, SPSS Inc., Munich, Germany). To determine the relationship between reproductive performance and mean serum cIGF1 in the postpartum period, cows were categorized as conceived after first, after second and greater service, or not pregnant despite being inseminated according to Taylor et al. (2004). The changes of mean serum cIGF1 in the 3 groups were compared using the univariate ANOVA procedure with repeated measurements and the Scheffe test as a post hoc procedure. To elucidate the relationships between the concentration of IGF1 in serum and reproductive performance in the current lactation (hypothesis 1), 3 different measures were analyzed. First, the relationships between a distinct cIGF1 measurement on a particular day (i.e., d 1, 4, 10, 20, and 40 pp); second, the cumulative cIGF1 in the postpartum period as described by the area under the curve (AUC) of those 5 measurements; and third, a linear regression coefficient (RC) based on 5 measurements of cIGF1. For the first (single cIGF1 measurements) and second (AUC) analysis, cows were categorized into quartiles according to cIGF1. For the third analysis a linear regression coefficient of the 5 individual measurements of cIGF1 was calculated to describe the slope of IGF1 in the postpartum period and cows categorized accordingly into 2 groups (positive or negative slope). To compare the

strength of the relationships of the different IGF1 measures and reproductive performance (hypothesis 2), 2 analyses were conducted. First, for the relationships of cIGF1 and days to pregnancy Pearson correlation coefficients were calculated and compared. Second, receiver operating characteristic (ROC) curve analysis was performed to compare the diagnostic performance of the different IGF1 measures in respect to their ability to discriminate between pregnant and nonpregnant cows. The values for the area under the ROC curve were calculated and compared.

Reproductive performance was characterized by days to first AI, first AI conception rate (number of cows pregnant after first AI divided by number of cows inseminated $\times$ 100), all AI conception rate (number of cows pregnant after all AIs divided by number of cows inseminated $\times$ 100), days to pregnancy, pregnancy rate (number of cows documented to be pregnant at 200 DIM divided by number of cows enrolled $\times$ 100), and proportion of cows culled up to 305 DIM. Cows not pregnant by 200 DIM were classified as not pregnant, even if they remained in the herd and conceived later in lactation. The proportion of cows diagnosed with endometritis at 20 to 26 d pp was also calculated.

Proportions were compared by Chi-square analysis. Days to first AI and days to pregnancy were compared by U-test (Mann-Whitney, Kruskal-Wallis test). Odds ratios and the 95% confidence intervals were calculated for the likelihood of study animals to conceive.

The relationship between average milk production within 10 d (i.e., 30 milkings) and cIGF1 in serum was described with the Pearson correlation coefficient. The greatest average milk production within 10 d in the 305-d lactation period was defined as greatest milk production (**10d AMP**). The cows were divided into quartiles regarding their greatest milk yield. The correlation between the mean cIGF1 and the peak milk yield was calculated using the univariate ANOVA procedure with repeated measurements and the Scheffe test as a post hoc procedure.

RESULTS

Reproductive Performance

Fifty cows (12.0%) were excluded from the analysis of reproductive performance because of culling and diseases. Of the remaining 367 animals, 121 cows conceived after first service (33.0%) and 170 after second or later services (46.3%), whereas 76 cows did not get pregnant within 200 d pp (20.7%). For all cows analyzed, first and all AI conception rates were 36.0 and 34.7%, respectively. Days to first AI, days to pregnancy, and pregnancy rate were 75.7 ± 19.0 ($n = 367$), $109.4 \pm$

43.9 ($n = 291$), and 73.3% ($n = 291$), respectively. The prevalence of endometritis was 25.6%.

Relationship Between Serum IGF1 and Conception Status

No significant difference in cIGF1 was found between cows that conceived after first service, after second or later services, or cows that did not get pregnant (Figure 1). In all groups cIGF1 increased from calving to 4 d pp and decreased from 4 to 10 d pp. From 10 to 40 d pp cIGF1 increased continuously. Cows that conceived after first service had significantly ($P < 0.05$) fewer days to first service (70.5 d) than cows that conceived after later services (76.8 d) and cows that did not conceive within 200 d pp (81.6 d, $P < 0.05$).

Relationship Between Reproductive Performance and Individual IGF1 Measurements

On d 1 and 4 pp reproductive performance traits were not statistically significantly different between the 4 IGF1 classes (data not shown). Only prevalence of endometritis was significantly greater on d 4 for cows in the lowest IGF1 quartile (38.8%) compared with the other quartiles (25.9, 19.2, 17.4%). On d 10 pp both conception rates were greater in cows with cIGF1 above the median ($P < 0.05$). The difference was not statistically significant for the all-AI conception rate in the fourth IGF1 quartile. Proportions of cows pregnant within 200 d pp and of cows with endometritis were lowest in cows classified into the first IGF1 quartile based on d 40 pp measurements (Table 1). Concentration of IGF1 was not related to the percentage of cows culled.

Relationship Between Reproductive Performance and Composite IGF1 Measurements

The median AUC of cumulative cIGF1 for all cows enrolled was $2,395.3 \text{ ng/mL}^2$ ($n = 417$). Both conception rates were significantly lower in cows below the median compared with cows above the median ($P < 0.05$). The proportion of cows pregnant within 200 d pp increased significantly from the first to the third IGF1 quartile (Table 2). The proportion of cows culled decreased from the first to the fourth IGF1 quartile. However, only the differences between the first (37.5%) and the other 3 IGF1 quartiles (26.7, 21.1, 19.2%) were statistically significant. Also, cows with greater AUC (second to fourth quartile) conceived earlier (11.4, 16.0, and 18.8 d) than cows in the first IGF1 quartile ($P < 0.05$). Survival analysis of number of services per preg-

Table 1. Descriptive statistics of reproductive performance in 389 multiparous cows classified according to concentration of IGF1 at 40 d postpartum.

Trait	1st quartile	2nd quartile	3rd quartile	4th quartile
Range of IGF1, ng/mL	<61.7	61.7–73.0	73.1–87.0	>87.0
Cows, n	97	98	98	96
Days to first AI	76.2 ± 20.9	74.9 ± 17.4	77.3 ± 19.2	75.8 ± 18.9
Days to pregnancy	112.6 ± 41.7	102.8 ± 39.6	104.4 ± 36.9	100.8 ± 40.6
First AI conception rate, %	31.9	32.9	34.9	32.6
All AI conception rate, %	35.2	32.7	34.8	31.2
Pregnancy rate, %	67.0 ^a	78.6 ^b	73.5 ^b	78.1 ^b
Cows with endometritis, %	20.6 ^a	26.5 ^b	23.5 ^a	28.1 ^b

^{a,b}Within a row, values with different superscripts differ ($P < 0.05$).

nancy did not reveal a statistical significant difference between the groups.

Relationship Between Reproductive Performance and Linear Regression Coefficient

A linear regression coefficient was calculated for all animals with a complete set of 5 measurements of cIGF1 ($n = 390$). A total of 27 cows had incomplete data sets because of culling and were excluded from this analysis. Based on the linear regression coefficient, 91 cows (23.3%) showed a negative slope and 299 cows (76.7%) showed a positive slope. No significant differ-

ences were found between these 2 groups for any of the reproductive performance traits.

Diagnostic Value of Different IGF1 Measures

Diagnostic values of the different IGF1 measures for reproductive performance are summarized in Table 3. The Pearson correlation revealed a significant relationship between all IGF1 measures and days to pregnancy except for the linear regression coefficient. However, the correlation coefficients were small and accounted for only 0.09% (RC) to 2.6% (AUC) of the variation of days to pregnancy. Also, ROC curve analysis dem-

Figure 1. Concentration of IGF1 in cows that conceived after first service ($n = 121$) and at later services ($n = 170$), and in cows that remained open despite services ($n = 76$).

Table 2. Descriptive statistics of reproductive performance in 417 multiparous cows classified according to cumulative concentration of IGF1 in the postpartum period as described by the area under the curve

Trait	1st quartile	2nd quartile	3rd quartile	4th quartile
Range of IGF1, ng/mL ²	<1,985	1,985–2,395	2,396–2,840	>2,840
Cows, n	104	105	104	104
Days to first AI	78.7 ± 20.8	75.2 ± 19.5	77.3 ± 17.9	72.4 ± 18.6
Days to pregnancy	117.0 ± 43.6 ^a	105.6 ± 37.6 ^b	101.0 ± 37.2 ^b	98.2 ± 39.5 ^b
First AI conception rate, %	27.6 ^a	30.8 ^a	39.4 ^b	43.6 ^b
All AI conception rate, %	30.7 ^a	32.3 ^a	37.4 ^b	38.4 ^b
Pregnancy rate, %	58.7 ^a	66.7 ^b	74.0 ^c	79.8 ^c
Cows with endometritis, %	34.2	33.1	29.2	29.3

^{a–c}Within a row, values with different superscripts differ ($P < 0.05$).

onstrated a low diagnostic performance of all IGF1 measures. Only the IGF1 concentration on d 40 had a marginal ability to distinguish between pregnant and nonpregnant cows. Differences in the strength of the relationship between IGF1 measures and reproductive performance were negligible. The 2 composite IGF1 measures were not superior compared with individual IGF1 measures.

Relationship Between Serum IGF1 and Milk Yield

Average 10-d milk production was 31.6 ± 4.8 kg ($n = 412$) for d 5 to 14 pp; 39.9 ± 5.5 kg ($n = 405$) for d 15 to 24 pp; 43.0 ± 5.5 kg ($n = 394$) for d 25 to 34 pp; and 44.0 ± 5.4 kg ($n = 389$) for d 35 to 44 pp. We could demonstrate a statistically significant negative correlation between cIGF1 at 10 d pp and the 10d AMP from 5 to 14 d pp ($r = -0.106$, $P = 0.04$). Furthermore, statistically significant differences were found between cIGF1 at 20 d pp and the 10d AMP from 15 to 24 d pp ($r = -0.189$, $P < 0.01$) as well as between cIGF1 at 40 d pp and the 10d AMP from 35 to 44 d pp ($r = -0.165$, $P < 0.01$). There were no significant correlations between cIGF1 at calving and the 10d AMP from 5 to 14 d pp ($r = -0.095$, $P = 0.46$) and between cIGF1 at 4 d pp and the 10d AMP from 5 to 14 d pp ($r = -0.074$, $P = 0.67$), respectively.

Cows in the greatest peak milk yield quartile during lactation had lower cIGF1 at all sampling times compared with cows in the lowest milk yield quartile (Table 4).

DISCUSSION

IGF1 and Reproductive Performance

It has been proposed that measurements of IGF1 in the postpartum period are valuable predictors for reproductive performance and may assist in the management of fertility in high-yielding dairy cows (Pushpakumara et al., 2003; Taylor et al., 2004; Patton et al., 2007). An upward trend of serum cIGF1 in the early postpartum period has been discussed as a requirement for early resumption of cyclicity in dairy cows and consequently improved fertility (Thatcher et al., 2006). The objective of our study was to evaluate different IGF1 measures—distinct IGF1 concentration on particular days pp, cumulative concentration (AUC), and linear regression coefficient based on 5 measurements—with regard to their predictive quality for reproductive performance.

The analysis of our data set including 411 multiparous cows did not reveal any significant differences in the mean serum IGF1 concentration between cows that conceived after first service (57.2 ± 12.7 ng/mL),

Table 3. Diagnostic performance of different IGF1 measures for reproductive performance as described by Pearson correlation coefficients for days to pregnancy and receiver operating characteristic (ROC) curve analysis for discrimination between pregnant and nonpregnant cows

IGF1 measure	Pearson correlation analysis		ROC curve analysis	
	Pearson correlation	Level of significance	Area under curve	95% confidence interval
Concentration on d 1	−0.12	0.05	0.50	0.44–0.55
Concentration on d 4	−0.15	0.01	0.51	0.46–0.56
Concentration on d 10	−0.14	0.02	0.55	0.50–0.60
Concentration on d 20	−0.12	0.04	0.54	0.49–0.59
Concentration on d 40	−0.12	0.04	0.56	0.51–0.61
Linear regression coefficient	0.03	0.61	0.56	0.51–0.61
Area under curve	−0.16	0.007	0.55	0.50–0.60

Table 4. Concentration of IGF1 of 358 multiparous cows grouped according to quartiles of peak milk production

Peak milk production (kg/d)	Concentration of IGF1 in serum at days postpartum (pp)				
	1 d pp	4 d pp	10 d pp	20 d pp	40 d pp
<41.7	61.3 ^b ± 23.3	69.9 ^b ± 33.5	57.9 ^b ± 23.7	72.3 ^b ± 27.0	83.3 ^b ± 22.4
n	105	103	100	96	80
41.8–45.1	56.7 ^a ± 15.8	60.3 ^{ab} ± 23.2	53.7 ^{ab} ± 19.0	63.6 ^{ab} ± 18.0	74.1 ^a ± 16.6
n	106	106	106	106	105
45.2–48.7	57.1 ^a ± 17.7	59.7 ^{ab} ± 23.0	52.5 ^{ab} ± 18.7	62.8 ^{ab} ± 18.0	72.9 ^a ± 19.5
n	99	99	99	99	98
>48.8	52.8 ^a ± 16.8	57.6 ^a ± 22.8	49.4 ^a ± 16.2	57.5 ^a ± 19.1	70.8 ^a ± 19.9
n	98	97	97	97	97

^{a,b}Within a column, different superscripts indicate significant differences between the groups ($P < 0.05$).

later service (52.7 ± 18.9 ng/mL), and cows that did not become pregnant (52.9 ± 18.7 ng/mL). In a study by Taylor et al. (2004) the mean concentration of IGF1 in plasma was 37.1, 32.7, and 20.2 ng/mL, respectively, for these 3 groups (group 1 vs. 3; $P < 0.05$). The slightly greater concentrations of IGF1 in our study might be due to differences in negative energy balance of the study populations or timing of blood sampling (d 10 ± 2 d vs. weekly after calving). Because the concentration of IGF1 increases in the postpartum period, an earlier sampling time would cause lower IGF1 concentrations.

A threshold of 25 ng/mL IGF1 in wk 1 pp has been suggested to distinguish between cows likely and unlikely to conceive to first service (Taylor et al., 2004). Our data do not confirm this observation. A survival analysis of proportion of pregnant cows did not show a statistically significant difference between cows with less than and greater than 25 ng/mL IGF1. However, in our study only 30 out of 411 animals (7.2%) had a concentration of IGF1 <25 ng/mL at 10 d pp.

Otherwise, our data provide additional evidence for a relationship between reproductive performance and IGF1 concentration. On d 10 pp, cows with a concentration of IGF1 less than the median had lower first- and all-service conception rates than the cows in the quartiles with a concentration greater than the median IGF1 concentration. This is in agreement with previous reports that described an association of IGF1 concentration in the first week after calving with conception rate to first service (Patton et al., 2007). Also, there was a continuous increase of the proportion of cows pregnant within 200 d pp and a steady decrease in days to pregnancy from the first to the fourth quartile of cumulative cIGF1. The positive effect of IGF1 in the early postpartum period on the quality of the oocytes (Jorritsma et al., 2003) could be an explanation for improved fertility of cows with greater cumulative concentrations of IGF1. Cows with high serum concentrations of IGF1 resumed estrus cyclic-

ity earlier and became pregnant faster than cows with a lower concentration of IGF1. The slope of the linear regression coefficient was not related to reproductive performance in our investigation as suggested earlier (Thatcher et al., 2006).

Our results confirm a relationship between the concentration of IGF1 in serum and reproductive performance in multiparous cows as described by others (Roberts et al., 1997; Taylor et al., 2004). However, the diagnostic performance of the 7 IGF1 measures for predicting fertility on an individual cow basis was low. Also, differences between the IGF1 measures regarding diagnostic performance were insignificant. Based on our data, IGF1 concentrations after calving cannot be used to support reproductive management decisions.

IGF1 and Milk Yield

The results of our study demonstrate a significant negative correlation between the concentration of IGF1 and the 10-d average milk production as well as the peak milk production in the current lactation. A negative correlation of cIGF1 with milk yield (Spicer et al., 1990) and with peak milk yield in the current lactation (Taylor et al., 2004; Wathes et al., 2007) has been reported previously. However, Wathes et al. (2007) reported no significant correlation between plasma cIGF1 and milk yield in primiparous cows. In multiparous cows, there was a negative correlation between plasma cIGF1 and milk yield in wk 4 pp ($r = -0.13$, $P < 0.05$). The same researchers, however, did find a positive correlation between plasma cIGF1 and milk production in wk 7 pp ($r = 0.15$, $P < 0.05$). These results suggest that there are differences in the control of tissue mobilization between primiparous and multiparous cows that may promote nutrient partitioning into growth as well as milk during the first lactation (Wathes et al., 2007).

High-yielding dairy cows have greater concentrations of GH after parturition. That causes greater fat

mobilization and availability of nutrients for milk production. This situation is associated with a resistance of the liver to GH and reduced IGF1 production in the hepatic tissue (Taylor et al., 2003).

CONCLUSIONS

This is the first study to evaluate the predictive quality of different IGF1 measures in the postpartum period for reproductive performance in lactating dairy cows. Our data provide further evidence for an association between IGF1 concentration after calving and reproductive performance. A previously reported threshold to distinguish between cows likely and unlikely to conceive to first service (25 ng/mL) could not be confirmed. Pearson correlations between IGF1 measures and days to pregnancy were significant but practically irrelevant. Diagnostic performance for individual cow fertility of all IGF1 measures tested was marginal. Also, differences between the IGF1 measures were negligible. Thus, the routine measurement of IGF1 after calving is neither practical nor economically justifiable for reproductive management in dairy cows.

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