Stellingen

1. Genetisch vitale biggen hebben een hogere overlevingskans omdat ze rijper zijn bij geboorte *(dit proefschrift)*

   Het woord "rijper" is gekozen, omdat "gematureerd" niet bestaat

2. De rijpheid van een big bij geboorte weegt zwaarder voor overleving dan zijn gewicht *(dit proefschrift)*

3. Enkelvoudige selectie op bigoverleving bij westerse rassen leidt uiteindelijk tot biggen die grote overeenkomst vertonen met Meishanbiggen *(Knol E.F. 2001. Genetic aspects of piglet survival. Ph.D. dissertation, Wageningen University; dit proefschrift)*

4. Publicatiebias kan leiden tot een verkeerd beeld van de werkelijkheid

   (publicatiebias: verschijnsel waarbij juist die onderzoeken gepubliceerd worden die iets nieuws opleveren, terwijl onderzoeken die bevestigen wat we al lang wisten niet voor publicatie in aanmerking komen)

5. Behandeling van onvruchtbare mannen door intracytoplasmatische sperma-injectie (ICSI) zonder voorafgaande genetische screening verhoogt het risico op het doorgeven van genetische afwijkingen aan het nageslacht *(Dorrepaal, C.A. en S.E. Buitendijk. 1998. Tijdschrift voor Verloskundigen, 12:856-860)*

6. Het zogenaamde hoogtechnologisch draagmoederschap, waarbij de biologische ouders hun eigen kind moeten adopteren, doet denken aan een rozenkweker die een kas huurt en vervolgens zijn eigen rozen terug moet kopen

7. Werknemers met een goed curriculum vitae zijn niet bang voor een reorganisatie

8. "And in the end, the love you take is equal to the love you make" *(Lennon-McCartney, uit The End, Abbey Road, 1969)*

Stellingen behorende bij het proefschrift:
"Biological aspects of genetic differences in piglet survival",
Jascha Leenhouwers,
Wageningen, 4 december 2001.

Biological Aspects of Genetic Differences in Piglet Survival

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Biological Aspects of Genetic Differences in Piglet Survival

Jascha Leenhouwers

Proefschrift
ter verkrijging van de graad van doctor
op gezag van de rector magnificus
van Wageningen Universiteit,
Prof. dr. ir. L. Speelman,
in het openbaar te verdedigen
op dinsdag 4 december 2001
des namiddags te half twee in de Aula.

Biological Aspects of Genetic Differences in Piglet Survival
Doctoral thesis

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Abstract. The objective of this thesis was to gain insight in the biological background of differences in the direct genetic (piglet) component of piglet survival. Estimations of the direct genetic component of piglet survival were obtained by calculation of estimated breeding values for piglet survival (EBVps), which predict survival from onset of farrowing until weaning. The results in this thesis show that differences in survival as a consequence of differences in EBVps are already apparent in the perinatal period (i.e. in the period around birth). Both farrowing survival and survival during the first days after birth significantly increase with increasing EBVps of the litter. Differences in the course of farrowing (i.e. duration of farrowing and birth intervals) do not account for EBVps-related differences in farrowing survival and postnatal survival. Increased postnatal survival with increasing EBVps is not due to differences in early piglet behavior, such as the time from birth until first colostrum uptake. Explanations for increasing farrowing survival and postnatal survival with increasing EBVps are more likely to be found in a higher degree of fetal development or maturity during late gestation. This is substantiated by increased relative organ weights (liver, adrenals, and small intestine), increased serum cortisol levels, increased glycogen reserves in liver and muscle, and an increased carcass fat percentage in litters with high EBVps. The strong positive relationship between fetal cortisol and EBVps possibly caused the majority of the observed differences in fetal development and maturity. Knowing that cortisol plays a major role in the preparation for the transition from intrauterine to extrauterine life, piglets with a higher genetic merit for piglet survival may have an improved ability to cope with hazards during birth and within the first days of life.
The results in this thesis contribute to our understanding of the practical consequences of selection for increased piglet survival.

Voorwoord

Toen ik vijf jaar geleden solliciteerde naar de positie van OIO op het voor u liggende onderzoek naar biggensterfte had ik nog nauwelijks een varken van dichtbij gezien. Het was dus wel verstandig om me na het sollicitatiegesprek even mee te nemen naar een varkensbedrijf. Toen Egbert Knol me daar een doodgeboren big in de handen drukte en ik vervolgens niet flauwviel of onpasselijk werd, was het snel bekeken: hier zou ik me de komende vier jaar wel mee bezig kunnen houden. Dat het uiteindelijk vijf jaar is geworden, heeft te maken met de varkenspest die in 1997 enigszins roet in het eten gooide. Alhoewel...daardoor heb ik wel mooi wat interessante onderzoekstripjes naar Frankrijk en Brazilië kunnen maken.

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Jascha

Contents

Chapter 1

General Introduction

Throughout the world, around 20% of the total number of piglets born per litter do not survive from late gestation until weaning (Bedrijfsvergelijking Siva-software B.V., 1999; PigCHAMP Breeding Herd Summary U.S.A., 2000). This high piglet mortality rate is unacceptable both from an economic and animal welfare point of view.

The birth process is the first stressful event for the piglet. On average, between 3-8% of the total number of piglets are delivered stillborn (Spicer et al., 1986; Daza et al., 1999; Marchant et al., 2000). The major cause of stillbirth is asphyxiation (Randall and Penny, 1967; Randall, 1971). Asphyxiation may be induced by decreased placental blood flow associated with uterus contractions, damage or breakage of the umbilical cord, or premature detachment of the placenta (Curtis, 1974; reviewed by English and Morrison, 1984). Piglets born in the later stages of farrowing have an increased risk to suffer from asphyxia, because of cumulative effects of successive uterus contractions, or higher risks of premature rupture of the umbilical cord or detachment of the placenta (Randall, 1972a; Randall, 1972b; reviewed by English and Wilkinson, 1982).

The percentage of live-born piglets that dies until weaning varies considerably, ranging from 5 to 30% (Bille et al., 1974; Spicer et al., 1986; Daza et al., 1999). On average, between 50-70% of these preweaning losses occur within the first three days after birth (Hutchinson et al., 1954; Pomeroy, 1960; Fahmy and Bernard, 1971; Marchant et al., 2000). Major causes of preweaning mortality are starvation and overlying by the sow. Together, these causes constitute about 75% of the total mortality during the first days of life (English and Smith, 1975; English and Wilkinson, 1982; Dyck and Swierstra, 1987). Other mortality causes are congenital abnormalities (e.g. splayleg and atresia ani), savaging by the sow, and diarrhea. Infectious diseases as a primary cause of death play a minor role in mortality until weaning, accounting for approximately 5% of deaths (reviewed by Vaillancourt and Tubbs, 1992).

The survival chance of a piglet from late gestation to weaning is influenced by a complex of various predisposing factors. The degree of late fetal development is an important predisposing factor for perinatal mortality (i.e. stillbirth and early preweaning mortality) (Pomeroy, 1960; reviewed by Van der Lende et al., 2001). Piglets with low birth weight have a higher chance to be stillborn and are more at risk to die of starvation due to their inability to compete with heavier littermates for colostrum (England, 1974; reviewed

by Fraser, 1990; Herpin et al., 1996). Low birth weight piglets are especially at risk if they are born in a large litter or in a litter with a high within-litter variation in birth weight (English and Smith, 1975). Specific developmental and maturational processes, such as the prenatal deposition of energy reserves (e.g. fat and glycogen) and late prenatal maturation of the gastrointestinal tract and lungs, are also likely to play a role in piglet survival (reviewed by Van der Lende et al., 2001).

Exposure to asphyxia during farrowing decreases the viability of live-born piglets, probably through reduced vigour and colostrum intake, as well as altered carbohydrate metabolism early after birth (Randall, 1971; Herpin et al., 1996; Herpin et al., 1999). Live-born piglets with a low viability are less able to adapt to extrauterine life and more liable to die from starvation or to be overlain by the sow.

The mothering ability of the sow also plays an important role in piglet survival. Various maternal behaviors are related to losses due to overlying. Examples of these behaviors are carefulness when lying down and responsiveness to distress calls of the piglets (Hutson et al., 1993; Wechsler and Hegglin, 1997). Production of colostrum and milk in adequate amounts and of sufficient quality is also of vital importance to meet nutritional demands of the piglets, but also for acquisition of passive immunity (Curtis and Bourne, 1971; Wilson, 1974; Le Dividich and Noblet, 1981).

With regard to environmental factors that influence piglet survival, the design of the farrowing accommodation plays an important role. Sows are placed in farrowing crates during farrowing and lactation, in order to minimize losses due to overlying (Phillips and Fraser, 1993). The provision of a comfortable thermal environment for the piglets is very important, because newborn piglets are very cold-sensitive, due to their poor insulation and limited amounts of energy reserves (reviewed by Le Dividich et al., 1998). According to Curtis (1974), chilling may be responsible for most piglet losses, because it predisposes piglets to overlying, starvation, and disease.

Piglet mortality can be reduced drastically when farrowings are supervised and individual care is given to piglets during the first days after birth. Holyoake et al. (1995) showed that supervision during farrowing and the first three days after birth reduced total mortality until weaning from 16.8% to 8.6%. In another study by White et al. (1996), an improved farrowing management protocol caused a reduction in total mortality from 18.2% to 10.1% in unattended litters compared to attended litters, respectively. However,

increasing herd sizes and the high costs of labour in Western countries make it impossible to supervise every farrowing. If no measures are taken, mortality rates are likely to increase even more in the future, due to increasing selection pressure on litter size and ongoing selection for lean tissue growth. Selection for increased litter size decreases birth weight with possible concomitant delayed maturation of the gut and central nervous system (Thornbury et al., 1993; Wise et al., 1997; Kaufmann et al., 2000). Selection for lean tissue growth may adversely affect physiological maturity at birth (Herpin et al., 1993).

These current developments in the pig industry led to the initiation of a research project to investigate genetic and biological aspects of piglet mortality. The work reported in this thesis represents the biological part of this project. The genetic aspects of piglet mortality have been described by Knol (2001). He has shown that piglet survival has a genetic component. Genetic selection for increased piglet survival is possible without decreasing litter size and without increasing birth weight. Both the direct genetic component (intrinsic vitality of the piglet) and the sow component (uterus quality and mothering ability) need to be considered in the genetic analysis of piglet survival.

Objective of this Thesis

The main objective of this thesis is to gain insight in the biological backgrounds of differences in the direct genetic (piglet) component of piglet survival. Knowledge of underlying biological mechanisms of genetic differences in piglet survival will lead to a better understanding of the consequences of selection. This may contribute to a more balanced selection strategy from a physiological point of view. Furthermore, knowledge on biological backgrounds of genetic differences in survival may lead to identification of underlying biological traits that show more genetic variation than the trait survival as such. This information may be used to speed up genetic progress in piglet survival.

Outline of this Thesis

The results of this thesis are presented in Chapters 2 to 5. In Chapter 2, a large data set of approximately 8,000 litters is statistically analyzed to examine whether stillbirth differences are present in different genetic lines of pig. In addition, relationships between stillbirth and

various other traits are analyzed. In Chapters 3 to 5, litters that differ in genetic merit for piglet survival are used to study the biological backgrounds of genetic differences in piglet survival. Chapter 3 investigates the moment of death in the perinatal period in relation to genetic merit for piglet survival. For this experiment, detailed information on stillbirth and early neonatal mortality was collected under on-farm conditions in litters with known genetic merit for piglet survival. The progress of farrowing and early postnatal behavior of piglets in relation to genetic merit for piglet survival are studied in Chapter 4. Data on the progress of farrowing and piglet behavior was collected under on-farm conditions in litters with known genetic merit for piglet survival. Relationships between various characteristics of late fetal development and genetic merit for piglet survival are investigated in Chapter 5. In this chapter, groups of litters differing substantially in genetic merit for piglet survival were compared in a detailed physiological experiment.

The General Discussion (Chapter 6) discusses the results of Chapters 2 to 5 and sums up general conclusions.

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Chapter 2

Analysis of stillbirth in different lines of pig

J I. Leenhouwers, T. van der Lende, and E. F. Knol

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Abstract

In order to examine genetic influences on stillbirth in the pig, records of 7817 litters, originating from two purebred dam lines (D1 and D2), one purebred sire line (S), and one two-way cross (D12), were analyzed. For each litter, number of stillbirths, parity of the dam, gestation length (GL), total number of piglets born (TNB), average birth weight of the litter (ABW), variation in birth weight within the litter (VBW) and preweaning mortality rate (PWM) were recorded. After adjustment for ABW, there were no significant line differences in both average birth weight of stillborn and live-born piglets. Number of stillbirths per litter did not differ between lines, neither before nor after adjustment for GL, TNB, ABW and VBW, but was significantly influenced by GL, TNB and ABW, and not by VBW. Number of stillborn piglets per litter increased with decreasing GL, increasing TNB and decreasing ABW. On average, number of stillborn piglets increased between the second and the fifth parity. After adjustment for number of live-born piglets per litter, there was a significant positive relationship between number of stillborn piglets per litter and number of live-born piglets that died before weaning. In conclusion, no line differences in stillbirth were found, but significant line differences in the relation of stillbirth with GL, TNB and ABW indicate a small underlying genetic influence. The positive relationship of number of stillbirths with preweaning mortality of live-borns indicates an overall lower viability of litters in which stillbirths occur.

Keywords: Pig Stillbirth; Line Differences; Birth Weight; Preweaning Mortality.

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Introduction

In The Netherlands, stillbirth losses have remained constant in recent years and currently average 0.7 piglets per litter (Bedrijfsvergelijking Siva-produkten, 1997). Of the piglets classified as stillbirths, an average of 70-75% dies during delivery, the remainder shortly before and after parturition (Glastonbury, 1977; Stein, 1990). The major cause of piglet loss during parturition is asphyxiation (Glastonbury, 1977; English and Morrison, 1984). Factors that increase the risk of stillbirth are prolonged duration of parturition, premature rupturing of the umbilical cord, birth in the last third of the birth order, litter size over 12 piglets, increasing parity of the sow and a sow hemoglobin concentration less than 9 g/100 mL of blood (Moore et al., 1965; Randall, 1972; Bille et al., 1974). Evidence for a genetic influence on stillbirth is provided by Ernst (1988) and Siewerdt and Cardellino (1996), who reported a heritability of stillbirth of 0.02-0.08 and by studies which report higher stillbirth rates in purebred than in crossbred litters (reviewed by Blasco et al., 1995). There have also been studies on between-breed variation in stillbirth and these are reviewed by Blasco et al. (1995). Legault (1985) reported elevated perinatal mortality rates in Piétrain gilts and to a lesser extent in Belgian Landrace gilts. Legault and Caritez (1983), Bidanel et al. (1989) and Bidanel (1993) found lower stillbirth rates in the Meishan breed, as compared to the Large White breed.

This study was conducted to examine whether stillbirth differences are present in different lines of pig and to investigate the relation of stillbirth with other traits. The objectives of this study were: (a) to compare the birth weight of stillborn and live-born piglets between lines; (b) to examine line differences in number of stillbirths per litter, before and after adjustment for gestation length, total number of piglets born, average birth weight of the litter and variation in birth weight within the litter; (c) to examine line differences in the relationship between stillbirth and each of the factors gestation length, total number of piglets born, average birth weight of the litter and variation in birth weight within the litter and (d) to analyze the relationship between stillbirth and subsequent preweaning mortality of live-born piglets.

Material and Methods

Data

Data used in this study were obtained from the pig breeding company Dalland, Venray, The Netherlands. The data were collected from January 1993 through October 1996 on 12 nucleus and multiplier pig farms, located in The Netherlands, Belgium and France. The data-collection procedure was similar on all farms, and the data were processed for further analysis by the Dalland breeding company.

Records of 7817 litters, produced by 4162 sows, were analyzed. The material used consisted of purebred litters of two dam lines (D1 and D2) and one sire line (S), and two-way crossbred litters (D12), produced by D2 dams mated by D1 sires. Line D1 was founded in 1968, originating from different Piétrain populations. Line D2 was founded in 1968, using animals from different Great Yorkshire and Large White populations available. These two lines have been closed for more than 25 years and are selected for growth, feed-intake, backfat thickness, meat quality and reproduction traits. Since 1989, lines D1 and D2 are selected as specialized dam lines with much heavier emphasis on female reproduction. Since 1993, line D1 is selected mainly on litter size and piglet vitality and only partly on growth, feed-intake and backfat thickness, and line D2 is solely selected on litter size and mothering ability. Line S is a specialized sire line since 1989 and was selected only on growth, feed-intake and backfat thickness until 1993 when piglet vitality was added to the breeding goal. Line S is a synthetic, founded in 1976 using selected animals from dam lines D1 and D2. Each line occurred on at least three farms and on nine of the 12 farms two or three lines were present.

For each litter, the number of stillborn piglets, gestation length (GL), total number of piglets born (TNB), average birth weight of the litter (ABW), variation in birth weight within the litter (VBW), parity of the sow and preweaning mortality rate (PWM) were recorded. A piglet was registered as stillborn when it showed no signs of decay and when it was found dead lying behind the sow at the first check up after parturition ($\leq$ 12 h after birth). GL was calculated as the difference between the day of first mating and the day of parturition. Litters with only stillborn piglets were included in the analysis. Mummified and degenerating piglets were excluded from TNB. Each piglet, alive or stillborn, was weighed and individually identified within 24 h after birth. Due to litters with no live-born piglets, the birth weight of live-borns had the following number of observations: n= 7810 litters (all

lines), 1172 litters (D1), 2032 litters (D2), 3432 litters (D12), 1174 litters (S). Due to litters with no stillborn piglets, the birth weight of stillborns had the following number of observations: n = 2614 litters (all lines), 394 litters (D1), 708 litters (D2), 1084 litters (D12), 428 litters (S). VBW was computed as the standard deviation of birth weight of TNB within a litter. Due to litters with TNB=1, VBW could only be computed for a limited number of litters: n=7800 litters (all lines), 1173 litters (D1), 2031 litters (D2), 3424 litters (D12), 1172 litters (S). PWM was defined as the percentage of live-born piglets that died during the preweaning period. The term litter is used, referring to all piglets born during one farrowing at the same time by the biological mother, i.e. including piglets that were crossfostered to another sow. Weaning took place at an average of 28 days. Only litters from sows in parities one to five were included in the analysis. Litters with a GL shorter than 108 days or longer than 119 days were excluded from the data set, because of low numbers of observations.

Statistical Analysis

Six models were used to analyze the data (Table 1). Models (1) and (2) were used to compare the birth weight of stillborn and live-born piglets between the different lines, both before (1) and after (2) simultaneous adjustment for ABW. Model (2) was also used to determine the relationship between ABW and the birth weight of stillborn and live-born piglets, respectively. Models (3) and (4) were used to analyze the number of stillbirths per litter for the different lines, before (3) and after (4) simultaneous adjustment for GL, TNB, ABW and VBW. Model (5) was used to analyze the relationship between number of stillbirths per litter and each of the factors GL, TNB, ABW and VBW for the different lines. The relationship between the number of stillbirths and preweaning mortality of live-born piglets within a litter was determined by model (6).

Models (1) and (2) were used for data analysis, using the general linear models procedure of Statistical Analyses System (SAS, 1990), and models (3), (4), (5), and (6) were used for data analysis by logistic regression, using Proc Genmod of SAS (1990). Analysis by logistic regression in models (3), (4), (5), and (6) was used because of the binomial distribution of stillbirth. The log probability of stillbirth is given by log (stillbirth rate/[1-stillbirth rate]), where stillbirth rate is the proportion of piglets stillborn per litter. In order to obtain adjusted stillbirth means, the least squares mean estimates of models (3), (4), (5), and (6) were computed using these models under Proc GLM (SAS, 1990).

Table 1. The six models used for data analysis

	Model					
	1	2	3	4	5	6
Dependent variable	$BW_{Sb/Lb}$	$BW_{Sb/Lb}$	Stillborn	Stillborn	Stillborn	PWM_{lb}
Parameter[a]						
μ	x	x	x	x	x	x
$Line_i$ (i=1,4)	x	x	x	x	x	x
$Farm_j$ (j=1,12)	x	x	x	x	x	x
$Year_k$ (k=1,4)	x	x	x	x	x	x
$Month_l$ (l=1,12)	x	x	x	x	x	x
$Parity_m$ (m=1,5)	x	x	x	x	x	x
Line × $parity_{im}$	x	x	x	x	x	x
Line × $year_{ik}$	x	x	x	x	x	x
e	x	x	x	x	x	x
GL_n (n=1,12)				x		
Line × GL_{in}				x		
TNB_o (o=1,14)				x		
Line × TNB_{io}				x		
ABW_p (p=1,12)		x		x		
Line × ABW_{ip}		x		x		
VBW_q (q=1,11)				x		
Line × VBW_{iq}				x		
Var					x	
Line × Var					x	
sb_r (r=1,6)						x
Line × sb_{ir}						x
lb_s (s=1,14)						x

$BW_{Sb/lb}$=average birth weight of stillborn or live-born piglets; Stillborn=number of stillbirths per litter; PWM_{lb}= number of live-born piglets per litter that die before weaning; [a]μ=fitted mean; e=random error; GL=gestation length; TNB=total number of piglets born; ABW=average birth weight of the litter; VBW=variation in birth weight within the litter; Var=GL, or TNB, or ABW, or VBW; sb=number of stillborn piglets per litter; lb=number of live-born piglets per litter. x=included in the model.

Litters with more than five stillborn piglets were grouped together in the fifth stillbirth (sb) class. TNB and live-birth (lb) classes lower than four and higher than 17 were grouped

in classes 4 and 17, respectively. ABW classes were calculated as the integer of ABW multiplied by 10. ABW classes lower than 10 and higher than 21 were grouped in classes 10 and 21, respectively. VBW ranged from 20-960 g. For VBW, classes of 40 g were formed and classes higher than 460 g were grouped in class 11.

Results

Means

Table 2 summarizes means and phenotypic standard deviations for unadjusted data for the various variables, including litter stillbirth and PWM. For the 7817 litters analyzed, the average TNB was 10.77 piglets, including an average of 0.57 stillborn piglets per litter. The average PWM was 11.1%.

Table 2. Characteristics of the litters used for analysis. Mean values ± standard deviations are given

		Line			
	All	D1	D2	D12	S
No. litters	7817	1174	2035	3434	1174
Avg parity	2.5	2.2	2.5	2.7	2.3
TNB	10.77±3.03	10.46±3.14	10.90±2.84	11.08±3.11	9.98±2.82
Stillborn, no.	0.57±1.06	0.57±1.02	0.61±1.14	0.53±1.01	0.65±1.07
PWM, %[a]	11.1±14.4	13.0±15.8	10.5±13.6	10.4±14.0	12.2±15.6
GL, d	114.6±1.7	116.0±1.6	113.9±1.5	114.3±1.5	115.2±1.7
ABW, kg	1.51±0.25	1.52±0.24	1.44±0.23	1.54±0.25	1.54±0.27
VBW, kg	0.27±0.09	0.26±0.09	0.27±0.09	0.29±0.09	0.27±0.10
BW[b] live-borns, kg	1.52±0.25	1.52±0.25	1.44±0.23	1.54±0.25	1.55±0.27
BW stillborns, kg	1.31±0.35	1.36±0.31	1.27±0.32	1.31±0.36	1.33±0.37

[a]PWM=preweaning mortality rate; [b]BW=birth weight. For other abbreviations see Table 1.

Birth Weight of Stillborn and Live-born Piglets

In Figure 1, the birth weight of stillborn and live-born piglets and the relation with ABW are shown for the different lines.

There were significant line differences in average birth weight of stillborn and live-born piglets per litter (stillborn: $P < 0.01$; live-born: $P < 0.001$) (model 1). However, after adjustment for ABW, lines were no longer significantly different (stillborn: $P = 0.7$; live-

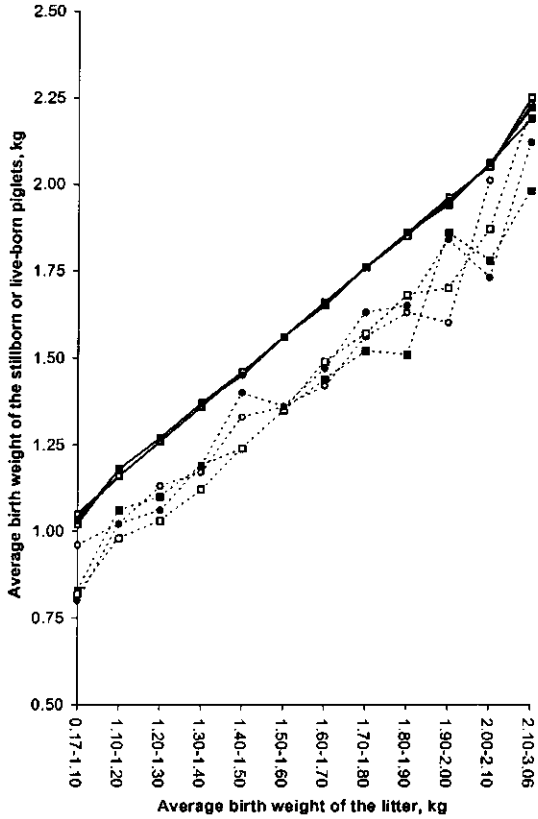

Figure 1. Relationship of average birth weight of the litter with the birth weight of the stillborn (sb) (dotted line) and live-born (lb) (solid line) piglets, respectively, for the different lines (O, D1; ■, D2; □, D12; ●, S)

born: $P = 0.09$) (model 2). A significant line × ABW interaction was found for both the birth weight of stillborn and live-born piglets (stillborn: $P < 0.01$; live-born: $P < 0.01$). From Figure 1 it can be seen that the average birth weight of the stillborn piglets within a litter is below that of the live-born piglets. As the ABW increased, the birth weight of stillborn and live-born piglets increased to the same extent. Consequently, the difference between the birth weight of stillborn and live-born piglets is independent of ABW ($P = 0.2$).

Line Differences in Number of Stillborn Piglets per Litter

Figure 2 shows the relation between parity and number of stillborn piglets per litter for the different lines. Before adjustment for GL, TNB, ABW and VBW (Figure 2a), the lines were not significantly different in number of stillborn piglets (P = 0.07) (model 3). In addition, the line × parity interaction was not significant (P = 0.10). On average, the number of stillborn piglets increased with parity, especially between the second and the fifth parity. After adjustment for GL, TNB, ABW and VBW (Figure 2b), lines were still not significantly different (P = 0.44) (model 4). The line × parity interaction remained not significant (P = 0.06).

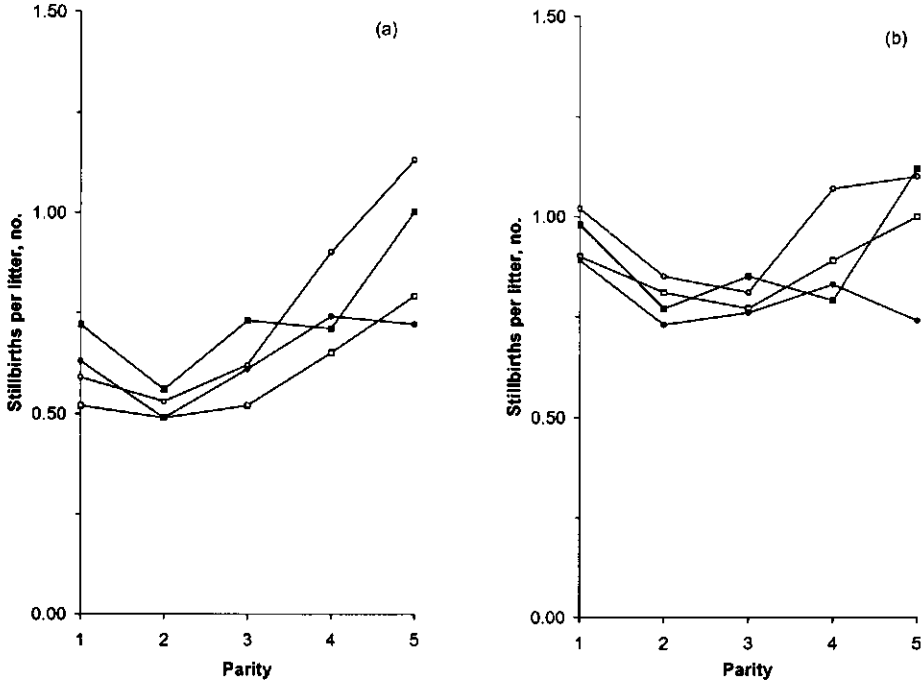

Figure 2. Effect of parity on the number of stillbirths per litter for the different lines (O, D1; ■, D2; □, D12; ●, S), before (a) and after (b) adjustment for GL, TNB, ABW and VBW.

Relationship Between Stillbirth and GL, TNB, ABW and VBW

The relationships between stillbirth and each of the factors GL, TNB, ABW and VBW are depicted in Figure 3. The number of stillborn piglets per litter was significantly influenced by GL (P < 0.001), TNB (P < 0.001) and ABW (P < 0.001), but not by VBW (P

= 0.27) (model 5). Apart from the interaction line × VBW ($P = 0.13$), the interactions line × GL ($P < 0.001$), line × TNB ($P < 0.01$) and line × ABW ($P < 0.01$) were all significant. The number of stillborn piglets per litter increased with decreasing GL, increasing TNB and decreasing ABW. Line D2 showed an increase in number of stillborn piglets per litter in litters with a high ABW (1.9-2.1 kg).

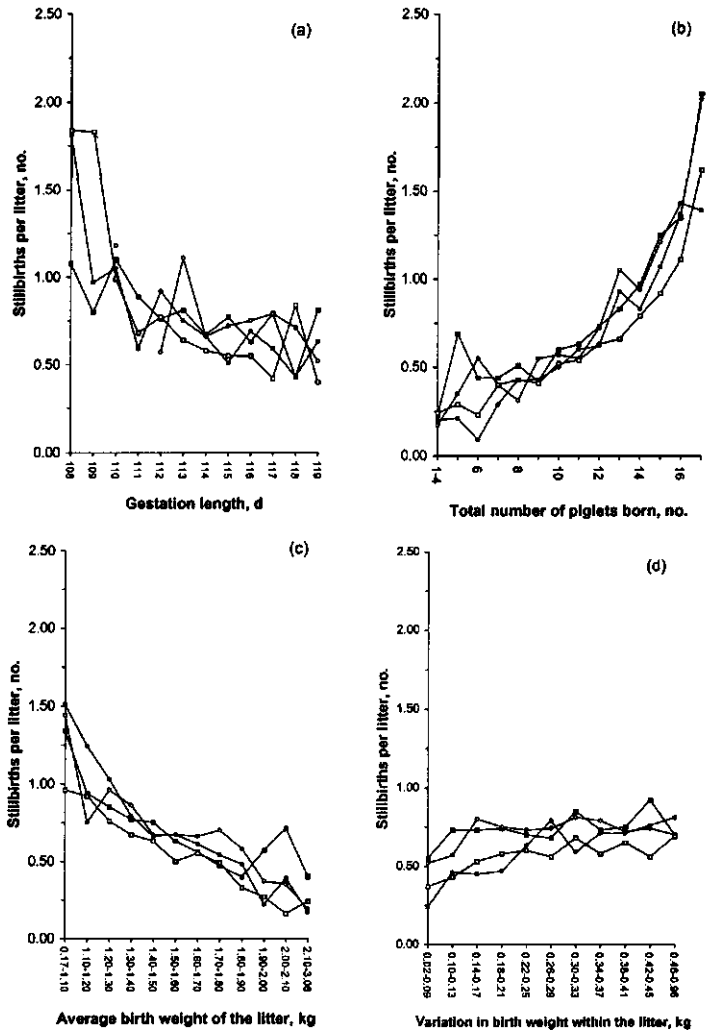

Figure 3. Effect of gestation length (a), total number of piglets born (b), average birth weight of the litter (c), and variation in birth weight within the litter (as given by the standard deviation) (d) on the number of stillbirths per litter for the different lines (O, D1; ■, D2; □, D12; ●, S). Note: Line D1 had no observations at GL=108, 109 and 111 days.

Relationship Between Stillbirth and Preweaning Mortality of Live-born Piglets

Figure 4 shows the relation between the number of stillborn piglets in a litter and the subsequent preweaning mortality of live-born piglets for the different lines. After adjustment for number of live-born piglets per litter, the preweaning mortality of live-born piglets per litter was significantly related to the number of stillborn piglets within that litter ($P < 0.001$) (model 6). However, the line × number of stillborn piglets per litter interaction was also significant ($P < 0.01$). When compared to the other lines, line D1 had a high preweaning mortality of live-born piglets within litters that contain zero, one or two stillborn piglets. This may explain the significant interaction of line with number of stillborn piglets per litter. On average, litters with more stillborn piglets also had a higher preweaning mortality of the piglets born alive.

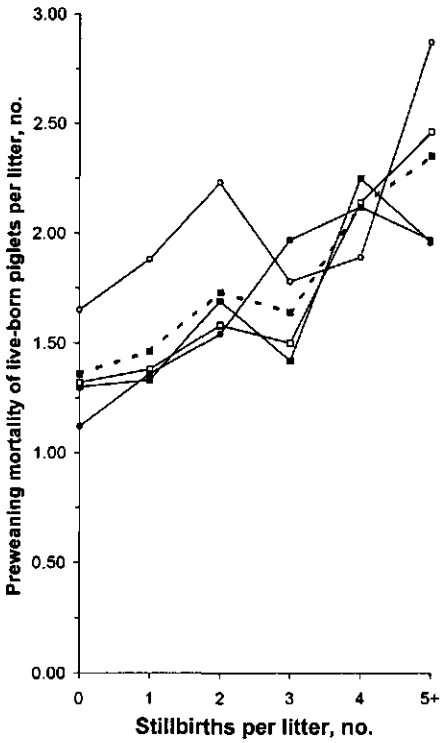

Figure 4. Relationship between the number of stillbirths per litter and preweaning mortality of live-born piglets for the different lines (O, D1; ■, D2; □, D12; ●, S) and for all the lines together (■, dotted line), after adjustment for the number of live-born piglets per litter.

Discussion

An average TNB of 10.77 piglets, 0.57 stillborn piglets per litter and a PWM of 11.1 % is in the range of figures published before (e.g. English and Wilkinson, 1982; Cutler et al., 1992; Bedrijfsvergelijking Siva-produkten, 1997).

Significant line differences in birth weight of stillborn, but also in birth weight of live-born piglets were found. However, these differences were caused by differences in ABW between lines, as they disappeared when ABW was included in model (2). The interaction of line with ABW was significant for both the birth weight of the stillborn and live-born piglets. Despite this, line differences at a given ABW were small: the relationship between ABW and birth weight of stillborn and live-born piglets was fairly similar for all lines.

The average birth weight of stillborn and live-born piglets both increased to the same extent with increasing ABW. Furthermore, for all lines and at every ABW, the average birth weight of the stillborn piglets was lower than that of the live-born piglets. These results imply the absence of an absolute threshold for birth weight, below which piglets have an increased chance to be stillborn. Apparently, on average the relatively lightest piglets within a litter have a higher risk to be stillborn. The lower birth weight of stillborn piglets as compared to live-borns has been reported in previous studies (De Roth and Downie, 1976; Spicer et al., 1986; Dyck and Swierstra, 1987; Leon and Madec, 1992). Piglets with a low birth weight may be less vigorous and may have an increased risk of being asphyxiated at birth, because the duration of expulsion of these piglets may have been prolonged due to inefficient uterine contractions (England, 1974; Elze, 1985; Lauterbach et al., 1987). Evidence for an increased risk to be stillborn for piglets with a low birth weight is also provided by this study.

Comparison of stillbirth incidence between purebred and crossbred litters has been reported before in literature (reviewed by Blasco et al., 1995). In general, crossbred litters of Landrace, Yorkshire, Piétrain, Large White and Meishan breeds have a lower stillbirth incidence than purebred litters (Skarman, 1961; Kirsch et al., 1963; Minkema et al., 1974; Bae and Park, 1985; Bidanel et al., 1989). In this study, Figure 3b shows that when the total number of piglets born is higher than 12, crossbred line D12 has a lower number of stillbirths per litter than the purebred lines D1, D2 and S. Moreover, for 3313 litters with 12 or more piglets, the purebred lines have significantly more stillbirths per litter than the crossbred line ($P < 0.05$; results not shown). Therefore, the results of the above mentioned

studies are confirmed in this study. The number of stillborn piglets per litter before adjustment for GL, TNB, ABW and VBW was almost significantly different ($P = 0.07$) between lines (model 3), and after adjustment for GL, TNB, ABW and VBW the line × parity interaction approached significance ($P = 0.06$) (model 4). These results and the results of the above mentioned studies on differences in stillbirth between purebred and crossbred litters, could imply that there is some genetic influence on the occurrence of stillbirth, and that line differences in number of stillborn piglets per litter may depend on the litter size or parity considered. On average, the number of stillborn piglets per litter increased after the second parity, but this trend was less obvious after adjustment for GL, TNB, ABW and VBW, indicating that these factors explain a part of the increase in stillbirth with parity. Increased stillbirth at higher parities is often observed and may also be related to excessive fatness of older sows, pathological changes in the reproductive tract and poor uterine muscle tone, all leading to a less efficient parturition process (Randall, 1972; Pejsak, 1984). A relatively high number of stillborn piglets per litter at the first parity is also frequently reported and may be caused by too narrow birth canals (Pejsak, 1984; Prime et al., 1987; Cutler et al., 1992).

Factors that influence the number of stillborn piglets per litter were GL, TNB and ABW. This is in agreement with previous reports (Randall, 1972; Zaleski and Hacker, 1993). In this study the phenotypic interrelationships between the factors GL, TNB, ABW and VBW have not been analyzed, but these interrelationships do exist (Omtvedt et al., 1965; Aumaitre et al., 1979; Garnett and Rahnefeld, 1979; Bonte et al., 1980; Vanstalle et al., 1980), and therefore influences of these factors on stillbirth are not independent of each other. This should be kept in mind in the interpretation of results shown in Figure 3.

On average, all lines have increased numbers of stillborn piglets per litter at short GL. The large variability between lines in number of stillbirths per litter at short GL, as seen in Figure 3a, is probably due to low numbers of observations. This variability may also have caused the significant line × GL interaction. The reason for a high stillbirth rate at short GL may be the relative immaturity of the piglets, as suggested by Zaleski and Hacker (1993).

In this study, the number of stillborn piglets per litter increased with increasing TNB for all lines. Although a significant line × TNB interaction was found, the relationship between TNB and number of stillborn piglets per litter was fairly similar for all lines (Figure 3b). Previous studies reported that an increased stillbirth rate with increasing TNB can be explained by the prolonged duration of parturition (Bille et al., 1974; Zaleski and Hacker,

1993). Some studies also report higher stillbirth rates in very small litters (Sharpe, 1966; Šovljanski et al., 1971), but this was not confirmed in this study.

An increased stillbirth rate with decreasing ABW is commonly reported in literature and this may be caused by an overall lower vigour of the litter at the onset of parturition (England, 1974; Zaleski and Hacker, 1993). For all lines, the number of stillborn piglets per litter decreased with increasing ABW, but for line D2, an increase in the stillbirth rate in very heavy litters was observed. This may be caused by a prolonged parturition process, due to expulsion difficulties with large piglets (Fahmy et al., 1978).

In agreement with the study of Zaleski and Hacker (1993), no influence of VBW could be found on the number of stillborn piglets per litter. However, for very uniform litters a somewhat lower stillbirth incidence can be observed.

No reports were found in literature about the relationship between the number of stillborn piglets within a litter and subsequent preweaning mortality of the live-born piglets. In this study, a significant positive relationship was found. This means that, on average, litters with more stillborn piglets will also have a higher preweaning mortality of live-born piglets, which may be explained by a general lower viability of those litters.

Conclusions

After analysis of a large dataset consisting of records for 7817 litters, no significant differences in stillbirth could be found between lines, including a cross amongst them. Although significant interactions of line with GL, TNB and ABW and a higher stillbirth incidence in purebred than in crossbred litters were found, the genetic influence on stillbirth seems to be small according to results from this study. However, the fact that no variation in stillbirth could be found between lines, does not exclude the existence of genetic variation within lines, as considerable within-line variation exists in the occurrence of stillbirth.

The influence of GL, TNB, ABW and the absence of an influence of VBW on the occurrence of stillbirth were previously reported and are confirmed by this study.

The increased occurrence of preweaning mortality of live-born piglets in litters with a high number of stillborn piglets may be explained by a general lower viability of the live-born piglets of those litters.

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Chapter 3

Stillbirth and early neonatal mortality in the pig in relation to genetic merit for piglet survival

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Abstract

The objective of this study was to determine which component of piglet losses from late gestation until 12 h after birth was related to genetic merit for piglet survival of the litter. Records of 336 litters, with known estimated breeding values for piglet survival from onset of farrowing until weaning (EBVps), were analyzed. EBVps was calculated as the average breeding value of the sire and the dam, and therefore all piglets within a litter had the same EBVps. For each litter, birth weights, number of stillborn piglets (classified as non-fresh stillborn, prepartum stillborn, intrapartum stillborn and postpartum stillborn), and number of live-born piglets that died until first check-up after farrowing (average 12 h postpartum) were registered. A decrease in mortality with increasing EBVps was observed for all mortality categories. This decrease was significant for number of non-fresh stillbirths (P = 0.003), prepartum stillbirths (P = 0.001), and intrapartum stillbirths (P = 0.007), but not for number of postpartum stillbirths (P = 0.35) and early neonatal mortality (P = 0.17). Decreased intrapartum stillbirth with increasing EBVps could be seen at all parities, but the probability of intrapartum stillbirth differed between parities. Reduced non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps was not related to differences in birth weights of stillborn piglets. In conclusion, the significant decrease in non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps indicates a role for piglet genes in the occurrence of these stillbirth categories.

Keywords: Pigs; Stillbirth; Neonatal Mortality; Genetic Merit.

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Introduction

Piglet mortality from onset of farrowing until weaning at 3-4 weeks averages 20-25% of fully developed piglets (Fahmy and Bernard, 1971; Bille et al., 1974; reviewed by Cutler et al., 1992). Reduction of this mortality has mainly been attempted through improving management strategies. However, piglet survival from onset of farrowing until weaning also has a genetic component (reviewed by Blasco et al., 1995). Selection for piglet survival is not yet incorporated on a large scale in breeding programs, because of assumed low heritabilities (0.05-0.10) for this trait (Blasco et al., 1995; Van Arendonk et al., 1996; Rothschild and Bidanel, 1998). However, recent studies have shown that the presence of substantial genetic variation for piglet survival may be used to reduce mortality from onset of farrowing until weaning (Van Arendonk et al., 1996; Knol, 2001). Registration of survival of individual piglets, recording of birth weights, information on crossfostering of individual piglets and parentage information allow the estimation of breeding values for piglet survival (EBVps). EBVps has predictive value for survival from onset of farrowing until weaning (Knol et al., 2001a).

Mortality from onset of farrowing until weaning can be divided into stillbirth and mortality of live-born piglets (neonatal mortality). Stillbirth can be further categorized on the basis of post-mortem examination, which enables discrimination between piglets that died before, during, or shortly (i.e. maximally a few hours) after farrowing (Randall and Penny, 1967; Glastonbury, 1977; Carr and Walton, 1995). Data on the timing of piglet mortality show that about 60% of total piglet losses are due to stillbirth and neonatal mortality during the first 24 h after farrowing (Marchant et al., 2000). Registration of detailed information on stillbirth and early neonatal mortality in groups of litters with known differences in EBVps provides opportunities to investigate whether those groups show differences in the occurrence and timing of mortality in the period around birth. Information of this study will improve our insight in the biological characteristics of litters that differ in genetic merit for piglet survival. Ultimately, this may contribute to our understanding of the changes that occur in underlying physiological processes as a consequence of selection for piglet survival.

The objective of this study was to determine which component of piglet losses from late gestation until 12 h after birth was related to genetic merit for piglet survival of the litter.

Subsequently, it was investigated whether survival differences related to genetic merit for piglet survival could be explained by differences in birth weight.

Material and Methods

Data

Data were collected on a nucleus pig farm of the TOPIGS breeding company (Vught, The Netherlands). This farm is located in Brouennes, France and uses a three-week farrowing system. Data were collected from November 1997 through April 2000, during ten farrowing periods. Records of 336 purebred litters, produced by 307 sows, were used. Sows, ranging from parities one to eight, were of two specialized dam lines D1 and D2. Since 1993, line D1 has been selected mainly for litter size and piglet survival and line D2 was solely selected on litter size and mothering ability. For a more detailed description of these lines, see Leenhouwers et al. (1999).

Management

Sows were individually housed and neck-tethered throughout gestation and lactation. For the last six or seven days before the calculated farrowing date, sows were transferred to farrowing crates. From the start of gestation until six days before the calculated farrowing date (assuming gestation length is 115 days), gilts were fed 2.6 kg of a conventional sow diet (3.2 Mcal DE/kg) per day. Higher parity sows received 2.9 kg of this diet per day. Depending on sow body condition, these amounts were varied. From six to two days before the calculated farrowing date, sows received 1.4 kg of feed per day. One day before the calculated farrowing date, they received 1.2 kg of feed per day. On the calculated farrowing date, still pregnant sows received 0.5 kg of feed. The first day after farrowing, sows received 1 kg of feed per day. The maximum amount of feed given during lactation depended on body condition of the sow, parity and the number of suckling piglets (0.4 kg of feed extra per piglet). Water was supplied ad libitum at all stages of gestation and lactation.

In total, 49% of all farrowings were induced. Induction of farrowing took place if sows showed no signs of approaching farrowing on or after the calculated farrowing date. Following birth, sows and litters were treated according to a management routine, that included weighing of all piglets (alive and stillborn) at first check-up after farrowing (on average 12 h postpartum), and individual registration of piglet mortality. Piglets were not

crossfostered until first check-up after farrowing. Farrowings were not supervised. In case sows were farrowing while stockpersons were doing their daily management routine in the farrowing house, piglets were transferred directly after birth to a separated heated area with cloth bedding until they were dry.

Litters

Estimation of Breeding Values for Piglet Survival

All 336 litters included in this study had known estimated breeding values for piglet survival (EBVps). Piglets within a litter had the same EBVps, calculated as the average breeding value of the sire and the dam. EBVps can be interpreted as deviations of the average survival probability and are expressed in percentages. The range of EBVps of the 336 litters was continuous and the difference between litters with the lowest and highest EBVps was 9.4%. This indicates an expected phenotypic difference in piglet survival from onset of farrowing until weaning of 9.4% between litters.

EBVps were estimated using an animal model, with direct (piglet) and nurse sow as animal effects. Piglet survival is defined as a binary trait, with a zero score for piglets dead before or at weaning, including stillborn piglets, and a score of 100 if alive at the day of weaning. Sex, birth weight of the piglets in classes of 100 gram, and litter size are taken as fixed effects, while litter effect of the natural mother of the piglets is taken as random effect. To avoid auto-correlative responses, results obtained in this experiment were ignored in the calculation of EBVps. Methods for estimation of breeding values for piglet survival were described in more detail by Knol et al. (2001b).

Mortality Registration and Other Characteristics

For each litter, total number of piglets born (TNB), number of stillborn piglets and number of live-born piglets that died until first check-up after farrowing (early neonatal mortality) were registered. Mummified piglets were excluded from TNB. A piglet was classified as stillborn when it was found dead lying behind the sow at first check-up after farrowing. In contrast to live-born piglets that died until first check-up after farrowing, stillborn piglets were wet and/or more or less covered with placental membranes. Stillborn piglets were further classified as non-fresh and fresh stillborn. Non-fresh stillborn piglets showed signs of degeneration, as evidenced by a (partial) brown skin color. These piglets probably died more than a week before onset of farrowing (Randall and Penny, 1967). Fresh stillborn piglets showed no external signs of decay. After post-mortem examination they

were further classified into three categories: (1) Prepartum stillbirths had the same brick-red color of all their abdominal organs due to haemolysis and autolysis, and died in utero in the days closely preceding farrowing (Bille et al., 1974); (2) Intrapartum stillbirths had a normal color of the abdominal organs but the presence of mucus and/or meconium in the trachea indicated that they died during farrowing; (3) Postpartum stillbirths had (partly) aerated lungs, but no colostrum in the stomach, and thus died shortly after birth.

The average birth weight of the litter (ABW) included all non-fresh stillborn, fresh stillborn and all live-born piglets, but excluded mummified piglets. Variation in birth weight within the litter was calculated as the standard deviation of birth weight of total number of piglets born (VBW_1), and of total number of live-born piglets (VBW_2). Gestation length (GL) was calculated as the difference between the day of first mating and the day of farrowing.

Statistical Analysis

Table 1 shows four models that were used to analyze the data on a litter basis. Models 1 and 2 analyzed stillbirth and early neonatal mortality in relation to EBVps. Relationships were analyzed by logistic regression, with correction for underdispersion or overdispersion, using Proc Genmod (SAS, 1990). Logistic regression was used because of the binomial distribution of stillbirth and early neonatal mortality. Stillbirth was analyzed as non-fresh stillborn and fresh stillborn. Fresh stillborn was also separately analyzed as prepartum stillborn, intrapartum stillborn, and postpartum stillborn. Stillbirth was analyzed as a proportion of the total number of piglets per litter and early neonatal mortality was analyzed as a proportion of the number of live-born piglets per litter. Relationships of ABW, VBW_1 and VBW_2 with EBVps were analyzed by model 3, using Proc GLM of SAS (1990). Average birth weights of the different classes of stillborn piglets in relation to EBVps were analyzed by model 4, using Proc GLM (SAS, 1990). These relationships were calculated before and after adjustment for average weight of live-born piglets. EBVps was included in the models as a continuous covariable.

Least squares means of birth weights per piglet status at first check-up after farrowing ($status_{firstcheck}$) were calculated by a model (using Proc GLM of SAS, 1990), that included the effects of sow, sex of the piglet and $status_{firstcheck}$. Individual birth weight was analyzed as the dependent variable and significance for piglet status was tested against the sow effect. $Status_{firstcheck}$ consisted of the following classes of piglets: non-fresh stillborn, prepartum stillborn, intrapartum stillborn, postpartum stillborn, live-born but dead at first check-up

Table 1. Four models used to analyze mortality and birth weight characteristics in relation to EBVps

	Model			
	1	2	3	4
Dependent variable[a]	Stillb. class/TNB	Early neon. mort./LB	ABW VBW_1 VBW_2	BWstillb.class
Parameter[b]				
μ	x	x	x	x
Line	x	x	x	x
Parity	x	x	x	x
Farrowing period	x	x	x	x
GL	x	x	x	x
TNB	x		x	x
LB		x		
ABW	x	x		
ABWlive-borns				(x)
Males	x	x	x	x
EBVps	x	x	x	x
e	x	x	x	x

[a]Stillb. class, number of non-fresh, fresh, prepartum, intrapartum, or postpartum stillborn piglets; TNB, total number of piglets born; early neon. mort., number of live-born piglets that died until first check-up after farrowing; LB, number of live-born piglets; ABW, average birth weight of the litter; VBW_1, variation in withinlitter birth weight of TNB; VBW_2, variation of within-litter birth weight of LB; BWstillb. class, average birth weight of non-fresh, prepartum, intrapartum or postpartum stillborn piglets; [b]μ, fitted mean; farrowing period, period during which data were collected; GL, gestation length; ABWlive-borns, average birth weight of live-born piglets; males, percentage of male piglets within the litter; EBVps, estimated breeding value for piglet survival of the litter; e, random error; x, included in the model.

after farrowing, and live-born and alive at first check-up after farrowing. Least squares means of birth weights per $status_{firstcheck}$ were also calculated for two classes of EBVps. Piglets from litters with EBVps higher than –1.65% (half of the total number of litters) were grouped in the EBVps-class 'high' (average EBVps was –0.40%). The remaining piglets were grouped in the EBVps-class 'low' (average EBVps was –2.89%). For these calculations, a model that included the effects of sow, sex of the piglet, $status_{firstcheck}$, EBVps-class and the interaction of $status_{firstcheck}$ with EBVps-class was used under Proc

GLM (SAS, 1990). In all analyses, stepwise elimination of non-significant effects ($P > 0.05$) was applied.

Results

Means

Table 2 shows means and standard deviations for characteristics of the 336 litters included in this study. In total, 121 litters (36%) did not have any mortality until first check-up after farrowing. Stillbirth occurred in 158 litters (47%) and early neonatal mortality occurred in 106 litters (31.5%). In total, 4017 piglets were born in 336 litters and 305 piglets (7.6%) were stillborn. From these 305 stillborn piglets, 262 piglets were subjected to a post-mortem examination. From these examined piglets, 30 piglets (11.5%) were diagnosed as non-fresh stillborn, and 232 (88.5%) were diagnosed as fresh stillborn. From these 232 fresh stillborn piglets, 14 piglets (6%) died prepartum, 175 (75%) died intrapartum and 43 (19%) died postpartum.

Table 2. Characteristics of the litters. Mean values ± standard deviations are given

Litter characteristic[a]	n	Mean ± Stdev
Parity	336	3.4 ± 1.9
GL, d	336	113.5 ± 1.2
TNB, no.	336	11.96 ± 3.05
Total stillborn, no.	336	0.91 ± 1.40
Non-fresh stillborn, no.	310[b]	0.10 ± 0.36
Fresh stillborn, no.	310[b]	0.76 ± 1.29
Prepartum stillborn, no.	310[b]	0.05 ± 0.23
Intrapartum stillborn, no.	310[b]	0.57 ± 1.05
Postpartum stillborn, no.	310[b]	0.14 ± 0.42
Early neonatal mortality, %	336	3.67 ± 6.39
ABW, kg	335[c]	1.49 ± 0.23
VBW_1, kg	335[c]	0.31 ± 0.10
VBW_2, kg	335[c]	0.30 ± 0.09

[a]Fresh stillborn, includes prepartum, intrapartum, and postpartum stillborn;

[b]post-mortem examination on stillborn piglets was not performed in 26 litters;

[c]piglet birth weights were missing in one litter. For other abbreviations see Table 1.

Stillbirth and Early Neonatal Mortality in Relation to EBVps

Table 3 shows logistic regression coefficients (estimates) and *P*-values for the relationships of stillbirth and early neonatal mortality with EBVps. These relationships are shown in Figure 1. The negative estimates indicate a decrease in mortality with increasing EBVps for all categories. The decrease in mortality was not significant for the number of postpartum stillbirths and early neonatal mortality. There was a significant decrease in the number non-fresh and prepartum stillbirths with increasing EBVps. However, the decrease in prepartum stillbirth with increasing EBVps did not have a large influence on the total mortality, due to the low incidence of this stillbirth category (Figure 1). The probability of intrapartum stillbirth was higher than all other stillbirth categories for the range of observed EBVps (Figure 1).

Table 3. Estimates and *P*-values of the relationships of the various mortality categories with EBVps

Dependent variable	Estimate[a]	*P*-value
Non-fresh stillborn[b]	-0.25	0.003
Fresh stillborn[bc]	-0.15	0.008
Prepartum stillborn[b]	-0.31	0.001
Intrapartum stillborn[b]	-0.16	0.007
Postpartum stillborn[b]	-0.074	0.35
Early neonatal mortality[d]	-0.083	0.17
Total mortality[be]	-0.13	0.002

[a]Estimates are logistic regression coefficients; [b]analyzed as the proportion of the total number of piglets born; [c]includes prepartum, intrapartum and postpartum stillbirths; [d]analyzed as the proportion of the number of live-born piglets; [e]includes non-fresh stillborn, fresh stillborn, and early neonatal mortality.

The relationship between the probability of intrapartum stillbirth and EBVps was dependent on the parity of the sow (Figure 2). The decrease in intrapartum stillbirth with increasing EBVps was observed at all parities. Furthermore, Figure 2 shows that the probability of intrapartum stillbirth was lower in second and third parity sows compared to first parity sows, and increased with increasing parity after the fourth parity.

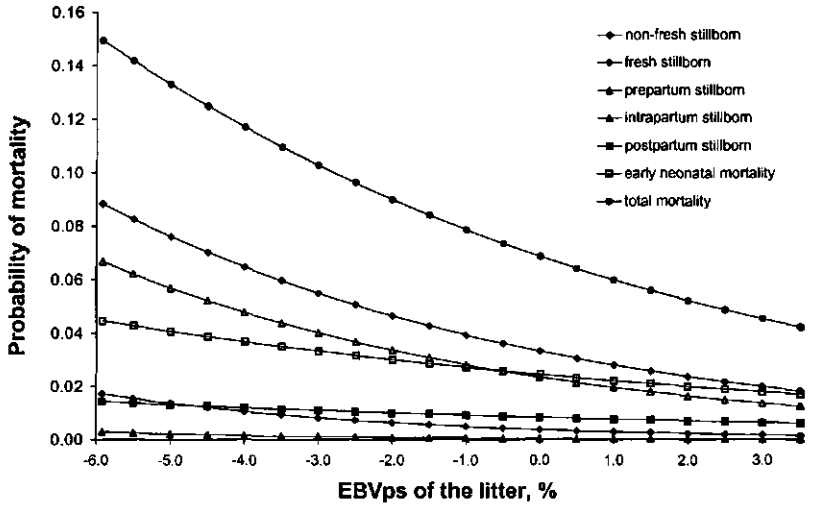

Figure 1. Probabilities of the various mortality categories in relation to EBVps of the litter. Note: Fresh stillborn includes prepartum, intrapartum and postpartum stillborn. Total mortality includes non-fresh stillborn, fresh stillborn, and early neonatal mortality.

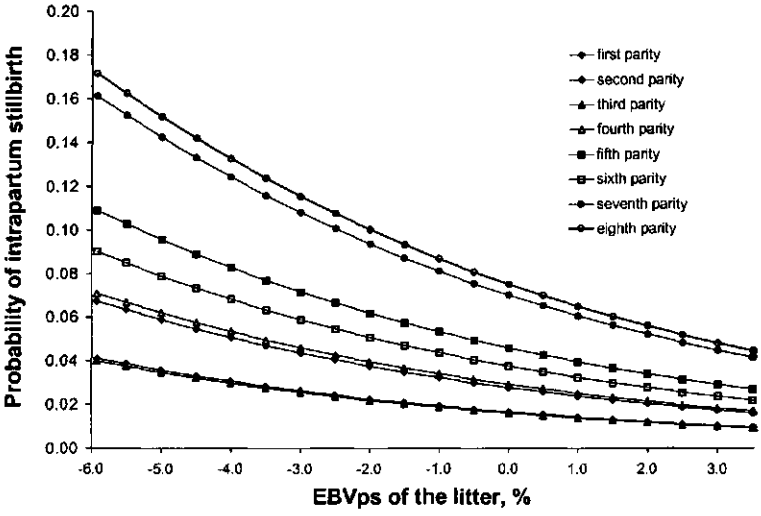

Figure 2. Probability of intrapartum stillbirth in relation to EBVps of the litter for the range of observed parities.

Birth Weights per Piglet Status at First Check-up After Farrowing and the Relation with EBVps

Birth Weights per Piglet Status

Table 4 shows least squares means of birth weights per piglet status at first check-up after farrowing ($status_{firstcheck}$). There were no significant differences in birth weights between the different categories of stillborn piglets. Live-born piglets that were dead at first check-up after farrowing were significantly lighter than the other categories, except for non-fresh and postpartum stillbirths. Piglets that were alive at first check-up were heavier than all other categories, except for prepartum stillbirths.

Table 4. Least squares means of birth weights per piglet status at first check-up after farrowing and the relation with EBVps

			BW per EBVps-class, g			
	n[1]	BW overall, g	n[1]	EBVps low[2]	n[1]	EBVps high[3]
$Status_{firstcheck}$[4]						
Non-fresh stillborn	30	1134^{ab}	17	1157^{ab}	13	1102^{ab}
Prepartum stillborn	14	1413^{bc}	8	1418^{abc}	6	1404^{abc}
Intrapartum stillborn	175	1253^{b}	106	1260^{b}	69	1237^{b}
Postpartum stillborn	43	1168^{ab}	21	1238^{ab}	22	1099^{ab}
Live-born, dead at first check-up	148	1063^{a}	82	1071^{a}	66	1051^{a}
Live-born, alive at first check-up	3564	1527^{c}	1766	1510^{c}	1798	1544^{c}

[1]Number of piglets; [2]average EBVps=-2.89%; [3]average EBVps=-0.40%; [4]status of the piglet at first check-up after farrowing; [a,b,c]comparisons were made between different classes of $status_{firstcheck}$. Birth weight means with different superscripts are significantly different at $P < 0.05$.

Birth Weights in Relation to EBVps

Average birth weight of the litter (ABW), variation in birth weight within the litter of total number born (VBW_1), and variation in birth weight of the litter of live-borns (VBW_2) were not related to EBVps (ABW: $P = 0.66$; VBW_1: $P = 0.43$; VBW_2: $P = 0.39$). Birth weights of stillborn piglets were not influenced by EBVps, neither before (non-fresh stillborn: $P = 0.10$; prepartum stillborn: $P = 0.76$; intrapartum stillborn: $P = 0.67$; postpartum stillborn: $P = 0.19$), nor after adjustment for birth weights of live-born piglets (non-fresh stillborn: $P = 0.44$; prepartum stillborn: $P = 0.76$; intrapartum stillborn: $P = 0.91$;

postpartum stillborn: $P = 0.19$). Table 4 shows that least squares means of birth weights per piglet status did not differ between stillborn piglets with a low or high EBVps.

Discussion

The reported stillbirth rate (7.6% of total number of piglets born) in the present study is in agreement with the range of values reported in literature (reviewed by Cutler et al., 1992). In this study we found that, in addition to stillbirth, almost 4% of live-born piglets died during the first 12 h after birth. These figures underline that the perinatal period accounts for a considerable amount of total piglet losses until weaning. In this study, post-mortem examinations demonstrated that most of the fresh stillborn piglets died intrapartum (75%). This is in agreement with the 70-90% range of intrapartum deaths described in literature (Randall and Penny, 1967; Randall, 1972; Bille et al., 1974; Glastonbury, 1977). The major cause of intrapartum stillbirth is fetal anoxia (Randall and Penny, 1967; Randall, 1971), which may be induced by decreased placental blood flow associated with uterine contractions, premature rupturing of the umbilical cord, or premature detachment of the placenta from the uterus (Curtis, 1974; reviewed by English and Morrison, 1984). Fetal anoxia probably also plays an important role in the etiology of postpartum stillbirth (Glastonbury, 1977). Factors influencing the occurrence of non-fresh and prepartum stillbirths are not always known (Glastonbury, 1977), but may include infection during pregnancy, iron deficiency of the sow (reviewed by English and Wilkinson, 1982), or failure of the placenta to meet nutritional demands of the growing foetus during late gestation.

The genetics of piglet survival can be analyzed on a maternal and a direct genetic level (Blasco et al., 1995). The maternal level relates to the genes of the sow and influences survival through uterus quality and mothering ability. The direct genetic level involves the genes of the piglets that influence their individual survival chances. In the present study, relationships are described, taking into account only the direct genetic component of piglet survival.

Selection for improved piglet survival on the basis of estimated breeding values for piglet survival will reduce overall mortality from onset of farrowing until weaning (Knol et al., 2001a). As most piglet deaths occur in the period around birth (reviewed by Svendsen, 1992), it is likely that selection against mortality will reduce mortality in this period. Our results show a decrease in mortality with increasing EBVps for all analyzed mortality

categories. Significant relationships of non-fresh and prepartum stillbirths with EBVps indicate a genetic basis for mortality occurring in late gestation. Intrapartum stillbirth was the largest stillbirth category and showed a very significant relationship with EBVps. As a consequence, the number of fresh stillbirths and total mortality (stillbirth and early neonatal mortality) also significantly decreased with increasing EBVps. Although decreased intrapartum stillbirth with increasing EBVps was evident at all parities, the level of stillbirth differed between various parities. The absence of a significant relationship of early neonatal mortality with EBVps may have been due to the relatively short period from birth to first check-up after farrowing (on average 12 h). Results from a previous study indicate that neonatal mortality up to three days after birth was indeed related to EBVps (Leenhouwers et al., 2001). In conclusion, these results imply that non-fresh, prepartum, and intrapartum stillbirth have a genetic basis, and are influenced by the genes of the piglet. Of course, this does not exclude an influence of the maternal genetic component of piglet survival on these stillbirth categories.

As this study was not performed under standardized conditions in an experimental unit, certain management practices may have influenced piglet survival. In the presence of a stockperson, piglets were transferred directly after birth to a heated area. As newborn piglets are very susceptible to cold (Le Dividich and Noblet, 1983), piglet survival could have been higher in litters where piglets were transferred, compared to litters where transfer did not occur. Relationships of survival with EBVps are not likely to be influenced by this human interference, because it took place independently of EBVps of the litter. Another management procedure that may have influenced piglet survival was the induction of farrowing in almost half of the litters studied. Farrowing was induced when sows did not show any signs of approaching farrowing on the calculated day of farrowing. Induction took place independently of EBVps of the litter, and therefore relationships of survival with EBVps were not influenced by induction of farrowing.

Birth weight plays an important role in piglet survival. Stillbirth and preweaning mortality both increase with decreasing birth weight (Sharpe, 1966; Leenhouwers et al., 1999; Roehe and Kalm, 2000). In this study, the birth weight of stillborn piglets and of live-born piglets that died until first check-up was significantly lower than the birth weight of live-born piglets that survived until first check-up. This indicates that lighter piglets somehow lack strength to withstand stress that is associated with the birth process, or otherwise have a reduced ability to adapt to the extrauterine environment (England, 1974;

Randall, 1992). Considering the relationship of stillbirth with birth weight, we investigated if the reduced number of non-fresh, prepartum, and intrapartum stillborn piglets in litters with high EBVps was related to birth weight. However, in our data we did not find any relation of weight of stillborn piglets with EBVps. This shows that birth weight is not an explaining factor for the reduced non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps.

The biological background of genetic differences in non-fresh and prepartum stillbirths are currently unknown. As mentioned earlier in the discussion, insufficient placental nutrient transfer to the foetus in late gestation may play a role in the etiology of non-fresh and prepartum stillbirth. However, the relatively high birth weights of prepartum stillborn piglets in the present study do not point towards placental insufficiency as an explanation for prepartum stillbirth. Results of a recent study of Wilson et al. (1999) suggest presence of genetic variation in placental efficiency, defined as birth weight divided by placental weight. It is possible that the observed decreased non-fresh stillbirth in litters with high EBVps may be related to a higher placental efficiency and consequently improved placental nutrient transfer in these litters.

Other biological factors than birth weight may explain the decreased intrapartum stillbirth in litters with high EBVps. In fetal lambs, the ability to survive anoxia is positively related to the initial concentration of cardiac carbohydrate (Dawes et al., 1959; Mott, 1961 in Shelley, 1961). Randall (1979) found that cardiac glycogen levels were significantly decreased in asphyxiated and stillborn piglets compared to unaffected littermates, suggesting a role for cardiac glycogen in the resistance against anoxia in the pig. In the present study, it is therefore possible that differences in the amount of cardiac carbohydrate could have accounted for a better intrapartum survival of litters with high EBVps.

Conclusions

Registration of stillbirth and early neonatal mortality in 336 litters with known genetic merit for piglet survival demonstrated the presence of genetic variation in the occurrence of piglet deaths in this period. Selection for improved piglet survival will lead to an overall reduction in stillbirth and early neonatal mortality. The present study reports a decrease in non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps. This indicates a role for piglet genes in the occurrence of these stillbirth categories. As reduced non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps could not be explained by differences in birth weight, other biological processes may play a role. Future research will be directed towards measurement of indicators for physiological maturity in litters with known genetic merit for piglet survival.

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Chapter 4

Progress of farrowing and early postnatal pig behavior in relation to genetic merit for pig survival

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Abstract

The objective of this study was to investigate whether pigs with different genetic merit for survival differed in birth weight, progress of farrowing, early postnatal behavior or rectal temperature within 24 h after birth. On a nucleus farm in Rio Verde, Brazil, information was collected on 280 pigs, originating from 25 litters with known estimated breeding values for pig survival (EBVps). Litters were selected in such a way that a continuous range of EBVps with a maximum genetic contrast was achieved. Birth weight was recorded for all pigs. Indicators for progress of farrowing were birth intervals and duration of farrowing. Behavioral indicators of pig vitality were time until first upright standing (FUS), time until first udder contact (FUC), time until first teat in mouth (FTM) and time until first colostrum uptake (FCU). Rectal temperature was measured within 24 h after birth. Farrowing survival and early postnatal survival (within 3 d after farrowing) were registered. Farrowing survival and early postnatal survival both increased with increasing EBVps (farrowing survival: $P = 0.007$; early postnatal survival: $P = 0.027$). Birth weight decreased with increasing EBVps ($P = 0.01$). Birth intervals tended to increase with increasing EBVps ($P = 0.10$) and duration of farrowing was not related to EBVps. Time until first teat in mouth increased with increasing EBVps ($P = 0.05$), but the other behavioral indicators of pig vitality were not related to EBVps. Rectal temperature within 24 h after birth was not related to EBVps. Pigs with a higher genetic merit for survival have a lower birth weight, but nevertheless have an increased farrowing survival and early postnatal survival. Their increased survival cannot be explained by differences in progress of farrowing, early postnatal behavior, or rectal temperature within 24 h after birth.

Keywords: Animal Breeding; Breeding Value; Farrowing; Perinatal Mortality; Pigs; Postnatal Development.

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Introduction

In general, 4 to 10% of the total number of pigs born die during farrowing, and 12 to 30% of live-born pigs die before weaning (reviewed by Cutler et al., 1992). A large variation in pig mortality exists between and within farms. This variation is mainly caused by management, but there is also substantial genetic variation (Van Arendonk et al., 1996). In populations with reliable registration of farrowing survival and pre-weaning survival, genetic variation can be quantified by the estimation of breeding values for pig survival (EBVps). Estimated breeding value for pig survival of an individual pig represents its genetic merit to survive from onset of farrowing until weaning.

From what is known about factors related to pig survival (Randall, 1972; Hoy et al., 1997; Le Dividich et al., 1998), estimated breeding values for pig survival of individual pigs may, among others, be related to birth weight, progress of farrowing, early postnatal pig behavior, or the ability to stabilize body temperature after birth. Information on these survival-related factors in pigs with known EBVps gives insight into the biological background of genetic differences in pig survival and will contribute to an improved selection and management strategy.

The objective of this study was to investigate whether pigs with different genetic merit for pig survival differed in birth weight, progress of farrowing, early postnatal behavior, or rectal temperature within 24 h after birth.

Material and Methods

Estimation of Breeding Values for Pig Survival

General

Since 1993, TOPIGS breeding company (Vught, The Netherlands) has used a registration protocol on 12 of their farms, including the farm reported in this study. This registration protocol involves individual weighing of all pigs at farrowing (including stillborn pigs, but excluding mummified pigs). Crossfostering of pigs is registered with identification of the nurse sow, as is date and cause of death in the case of failed survival. From the data set that results from this registration protocol, EBVps are estimated using an animal model, with direct (pig) and nurse sow as animal effects. Pig survival is defined as a binary trait, with a zero score for pigs dead before or at weaning, including stillborn pigs, and a score of 100 if alive at the day of weaning. Sex, birth weight of the pigs in classes of 100 gram, and litter size are taken as fixed effects, whereas the litter effect of the natural mother of the pigs is taken as a random effect. Estimated breeding values for pig survival can be interpreted as deviations of the average survival probability and are expressed in percentages.

Choice of Litters for This Experiment

This experiment was conducted on a TOPIGS nucleus pig farm in Rio Verde, Brazil. From the available litters on the farm, 25 litters were chosen on the basis of the pedigree index (the average breeding value of sire and dam) for direct effect of pig survival. Litters were chosen in such a way that a continuous range of EBVps with a maximum genetic contrast would be achieved. One year after completion of this experiment, EBVps of the 25 litters were estimated again on the basis of all then available information, ignoring results obtained in this experiment. This was beneficial for the accuracy of the breeding values. After renewed estimation, the range of EBVps was still continuous and the difference in EBVps between litters with the lowest and highest EBVps was 7.4%. This indicates an expected phenotypic difference in pig survival from onset of farrowing until weaning of 7.4%.

Data Collection

Animals

Data were collected on 280 pigs, originating from purebred litters of 25 sows, ranging from parities one to six (average parity: 3.1; SD = 2.1). All sows were of a specialized dam line D1 of the TOPIGS breeding company. Line D1 was founded in 1968, originating from different Piétrain populations. This line has been closed for more than 25 yr and was selected for an index including growth, feed intake, backfat thickness and meat quality. Since 1993, line D1 has been selected mainly for litter size and pig survival and only partly for growth, feed-intake and backfat thickness.

Housing and Feeding

At least 1 d before expected farrowing, sows were transported to the farrowing accommodation, which consisted of six farrowing houses that each contained 14 farrowing crates. The farrowing houses were enclosed by walls on the short sides and had wire netting on the long sides. In the presence of draughts and during the night, the long sides were covered by pulling up synthetic curtains. The average ambient temperature in the farrowing houses was 27 °C (range 21 to 32 °C). The farrowing crates (2.2 × 1.8 m) contained a 84-cm-wide area for the sow and two 48-cm-wide areas on either side of the sow for the pigs. The flooring in the area of the sow was a combination of metal grid and concrete. The area for the pigs was covered with solid plastic flooring. The pigs had access to a separated area (0.5 × 1.8 m) that had straw bedding and was heated by one 150-W lamp. Before the sows were housed in the farrowing crates, they were fed between 2.4 and 4 kg daily of a conventional sow diet, depending on body condition. In the farrowing crates, sows were fed 0.75 kg twice daily (0900 and 1600). On or after the calculated farrowing date, the sows were fed 0.5 kg twice daily. Sows received no feed on the actual day of farrowing or when they showed typical pre-farrowing behavior (reviewed by Fraser, 1984). During lactation, the sows were fed a conventional lactation diet. The composition of the lactation diet was similar for all sows, and the amount was varied according to parity of the sow and the number of suckling pigs. Water was supplied for ad libitum consumption at all stages of gestation and lactation.

Observation of Farrowing

All sows farrowed spontaneously. Observation of farrowing started when the sow showed clear signs of approaching farrowing (i.e., secretion of colored mucus from the vulva) and stopped when all pigs had consumed colostrum for the first time. Time of birth for each pig was recorded. Progress of farrowing was quantified by the characteristics birth interval and duration of farrowing. Birth interval for a pig was calculated as the time of its birth minus the time of birth of its preceding littermate. By definition, firstborn pigs did not have a birth interval. Duration of farrowing was calculated as the time interval between the birth of the first and last pig of the litter. Five sows farrowed stillborn pigs more than 24 h after farrowing started. In these cases, duration of farrowing was calculated as the time interval between the birth of the first and last pig of the litter within the period of observation of farrowing. For individual recognition, each pig was marked directly after birth by touching the pig gently with a color-marking crayon on the head or on the back. Subsequently, the following behavioral indicators of pig vitality were recorded: time of first upright standing (FUS), time of first udder contact (FUC), time of first teat in mouth (FTM) and time of first colostrum uptake (FCU). In total, 18 pigs from 11 litters (7% of all pigs born alive) did not have records for one or more of the behavioral indicators of pig vitality within the time of observation of farrowing. These pigs showed no motivation to drink, and therefore observation periods became excessively long. These pigs were nevertheless included in the analysis and for one or more of the behavioral indicators, they were assigned the time interval from their respective birth until the moment that observation of farrowing was stopped. This time interval was at least 85 min and at the most 382 min.

Other Data Collection

After observation of farrowing, pigs were briefly separated from the sow while their sex and birth weight were determined. Stillborn pigs were also weighed. Pig rectal temperature was measured within 24 h after birth. The moment of measurement of rectal temperature varied among pigs, but this moment was always recorded. The interval between the moment of birth and measurement of rectal temperature was taken into account when analyzing relationships of survival and EBVps with rectal temperature. Farrowing survival and postnatal survival before d 3 (early postnatal survival) were recorded for each individual pig. Considering the objectives of this study, farrowings were not assisted, pigs were not cross-fostered and early postnatal mortality was not prevented by human interference.

Gestation length was calculated as the difference between the day of first mating and the day of farrowing. Mummified pigs were excluded from the total number of pigs born. Average birth weight of the litter included stillborn and live-born pigs.

Statistical Analysis

Data obtained in this study were analyzed in three steps.

Step 1. Farrowing Survival and Early Postnatal Survival in Relation to EBVps

In the first model (model 1), farrowing survival and early postnatal survival were analyzed as dependent variables and are observations on the pig. Analysis was done by logistic regression, using the macro Glimmix (Littell et al., 1996). Logistic regression was used because of the binomial distribution of farrowing survival and early postnatal survival. The relation of survival with EBVps was analyzed with a model including the following effects: sow (included as a random effect), sex of the pig and birth weight (linear and quadratic).

Step 2. Farrowing Survival and Early Postnatal Survival in Relation to Birth Weight, Birth Interval, Duration of Farrowing, Behavioral Indicators of Pig Vitality, and Rectal Temperature

Table 1 shows the models that were used to analyze the relationships of farrowing survival and(or) early postnatal survival with birth weight (model 2), birth interval (model 3), duration of farrowing (model 4), behavioral indicators of pig vitality (model 5), and rectal temperature (model 6). Farrowing survival or early postnatal survival were analyzed as dependent variables and are observations on the pig. All relationships were analyzed by logistic regression, using the macro Glimmix (Littell et al., 1996).

Step 3. Birth Weight, Birth Interval, Duration of Farrowing, Behavioral Indicators of Pig Vitality, and Rectal Temperature in Relation to EBVps

Table 2 depicts the models that were used to analyze the relationships of birth weight (model 7), birth interval (model 8), behavioral indicators of pig vitality (model 9), and rectal temperature (model 10) with EBVps. Birth weight, birth interval, behavioral indicators of pig vitality, and rectal temperature were analyzed as dependent variables and are

observations on the pig. All relationships were analyzed using the GLM procedure of SAS (SAS Inst. Inc., Cary, NC). Log transformations of birth interval and all behavioral indicators of pig vitality were applied to obtain normally distributed residuals. Significance of (co)variables was tested against the sow effect.

Model (11) analyzed the relationship of duration of farrowing with EBVps on a litter basis, using the GLM procedure of SAS. Duration of farrowing was analyzed as the dependent variable and adjustments were made for the following effects: parity of the sow, gestation length, total number of pigs born, average birth weight of the litter, and the percentage of male pigs within the litter.

In models (1) to (11), stepwise elimination of nonsignificant ($P > 0.05$) (co)variables was applied.

Table 1. Models used to analyze the relationships of farrowing survival and early postnatal survival with birth weight, birth interval, duration of farrowing, behavioral indicators of pig vitality, and rectal temperature

	Model[b]				
Variable[a]	2	3	4	5	6
μ	x	x	x	x	x
Sow	x	x	x	x	x
Sex of the pig	x	x	x	x	x
Birth weight	x	x	x	x	x
Birth weight × Birth weight	x	x	x	x	x
Time rectal temperature-birth					x
Birth interval		x			
Duration of farrowing			x		
Behavioral indicators of pig vitality				x	
Rectal temperature					x
e	x	x	x	x	x

[a] μ, fitted mean; Time rectal temperature-birth, time interval between measurement of rectal temperature and moment of birth of the pig; e, random error; x indicates the variable was included in the model. [b] In models 2 to 4, both farrowing survival and early postnatal survival were analyzed as dependent variables. In models 5 and 6, only early postnatal survival was analyzed as the dependent variable.

Table 2. Models used to analyze the relationships of birth weight, birth interval, behavioral indicators of pig vitality, and rectal temperature with EBVps

	Model and dependent variable			
	7	8	9	10
Variable[a]	Birth weight	Birth interval	Behavioral indicators of pig vitality	Rectal temperature
μ	x	x	x	x
Sow	x	x	x	x
Sex of the pig	x	x	x	x
Birth weight		x	x	x
Birth weight × Birth weight		x	x	x
Time rectal temperature-birth				x
EBVps	x	x	x	x
e	x	x	x	x

[a] μ, fitted mean; EBVps, estimated breeding value for pig survival; Time rectal temperature-birth, time interval between measurement of rectal temperature and moment of birth of the pig; e, random error; x indicates the variable was included in the model.

Results

Descriptive Statistics

In this experiment, gestation length averaged 117.1 d (SD = 1.5 d). The average litter size was 11.2 pigs (SD = 3.0 pigs), of which 8.4% was stillborn. Of live-born pigs, 6.8% died within the first 3 d after birth. The average duration of farrowing was 3.5 h (SD = 2.5 h). Table 3 shows descriptive statistics for traits that were measured as observations on the pigs: birth weight, birth interval, the four behavioral indicators of pig vitality, and rectal temperature. Median values are given, because some distributions are extremely skewed. The last column of Table 3 shows the percentage of variation in the respective trait that can be attributed to differences between litters. For instance, 41% of the differences seen in birth weight are caused by differences between litters.

Table 3. Descriptive statistics for traits that were observed on the pigs

Trait[b]	n[a]	$\bar{x}$	Min	Max	Median	Between-litter variation, %
Birth weight, g	274	1518	450	2600	1500	41
Birth interval, min	245	19.1	0	175	10	26
FUS, min	251	8.9	1	56	7	14
FUC, min	257	23.1	3	240	14	13
FTM, min	256	52.7	5	382	28	15
FCU, min	258	69.4	6	382	44	18
Rectal temperature, °C	252	38.5	35.4	40.2	38.5	55

[a]Number of pigs. [b]FUS, time until first upright standing; FUC, time until first udder contact; FTM, time until first teat in mouth; FCU, time until first colostrum uptake.

Farrowing Survival and Early Postnatal Survival in Relation to EBVps

Farrowing survival and early postnatal survival both increased with increasing EBVps (farrowing survival: $P = 0.007$; early postnatal survival: $P = 0.027$). Estimates (logistic regression coefficients) for farrowing survival and early postnatal survival were 0.38 and 0.50, respectively.

Farrowing Survival and Early Postnatal Survival in Relation to Birth Weight, Birth Interval, Duration of Farrowing, Behavioral Indicators of Pig Vitality, and Rectal Temperature

Relationships of farrowing survival and early postnatal survival with birth weight, birth interval, duration of farrowing, behavioral indicators of pig vitality and rectal temperature are shown in Table 4. Farrowing survival was not related to birth weight, birth interval, or duration of farrowing. Early postnatal survival increased with increasing birth weight and decreasing duration of farrowing and was not related to birth interval. Early postnatal survival increased with decreasing FUC, decreasing FTM, and decreasing FCU but was not related to FUS and rectal temperature. The relationship of early postnatal survival with FCU for three different birth weights is shown in Figure 1. It is evident that, especially in smaller pigs (0.75 kg), survival chances decrease considerably with increasing FCU. Relationships of early postnatal survival with FUC and FTM were essentially similar.

Table 4. Relationships of farrowing survival and early postnatal survival with birth weight, birth interval, duration of farrowing, behavioral indicators of pig vitality, and rectal temperature

	Farrowing survival		Early postnatal survival	
Independent variable[a]	Estimate[b]	*P*-value	Estimate[b]	*P*-value
Birth weight, g	0.0008	0.15	0.013	0.0001
Birth interval, min	-0.010	0.13	0.005	0.76
Duration of farrowing, min	-0.002	0.24	-0.004	0.047
FUS, min			-0.015	0.66
FUC, min			-0.014	0.094
FTM, min			-0.016	0.0003
FCU, min			-0.015	0.0009
Rectal temperature, °C			0.39	0.32

[a]FUS, time until first upright standing; FUC, time until first udder contact; FTM, time until first teat in mouth; FCU, time until first colostrum uptake. [b]Estimates are logistic regression coefficients.

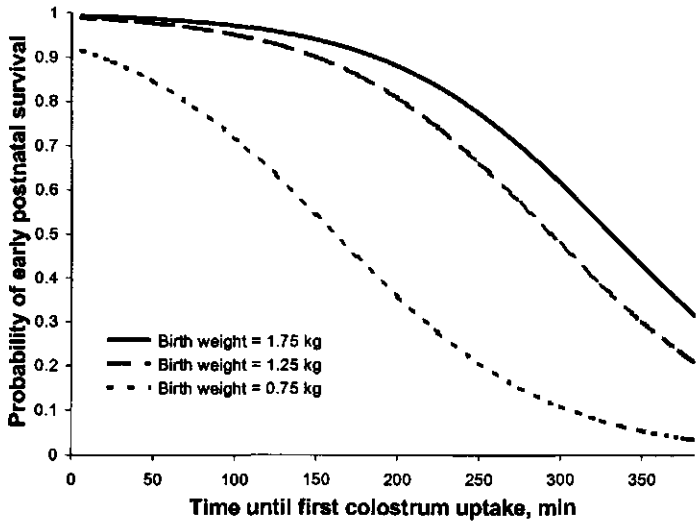

Figure 1. Relationship between the probability of early postnatal survival and the time until first colostrum uptake for pigs with birth weights of, respectively, 0.75, 1.25, and 1.75 kg. Relationships are calculated after adjustment for birth weight and are shown for the observed range in time until first colostrum uptake (6 to 382 min).

Birth Weight, Birth Interval, Duration of Farrowing, Behavioral Indicators of Pig Vitality, and Rectal Temperature in Relation to EBVps

The relationships of birth weight, birth interval, duration of farrowing, behavioral indicators of pig vitality, and rectal temperature with EBVps are shown in Table 5. Birth weight decreased with increasing EBVps. The relationship of early postnatal survival with birth weight for pigs with the lowest(-4.92%), highest (+2.46%) and average (-0.81%) EBVps is shown in Figure 2. The largest differences in early postnatal survival between pigs with the lowest and highest EBVps can be seen below a birth weight of approximately 1.50 kg. Birth interval tends to increase with increasing EBVps. Duration of farrowing was not related to EBVps. Time until first teat in mouth increased with increasing EBVps, but the other behavioral indicators of pig vitality were not related to EBVps. Rectal temperature within 24 h after birth did not show any relationship to EBVps.

Table 5. Relationships of birth weight, birth interval, duration of farrowing, behavioral indicators of pig vitality, and rectal temperature with estimated breeding value for pig survival

Dependent variable[a]	Estimate[b]	*P*-value
Birth weight, g	-131	0.01
Birth interval, min	0.41	0.10
Duration of farrowing, min	-25.7	0.14
FUS, min	-0.15	0.90
FUC, min	-0.275	0.74
FTM, min	0.10	0.05
FCU, min	0.21	0.15
Rectal temperature, °C	-0.11	0.91

[a]FUS, time until first upright standing; FUC, time until first udder contact; FTM, time until first teat in mouth; FCU, time until first colostrum uptake.[b]Estimates indicate the increase or decrease in the respective dependent variable with every percentage increase in estimated breeding value for pig survival.

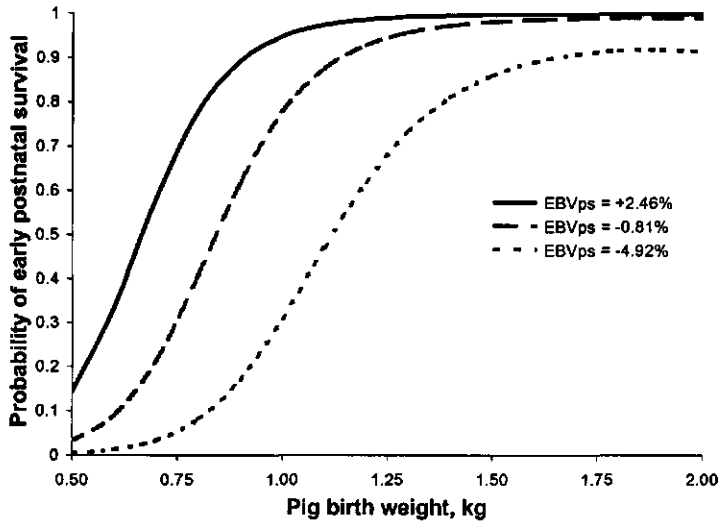

Figure 2. Relationship between the probability of early postnatal survival and pig birth weight for pigs with the lowest (-4.92%), highest (+2.46%), and average (-0.81%) estimated breeding values for pig survival (EBVps).

Discussion

Pig survival from onset of farrowing until weaning has a genetic and environmental component. Estimations of the genetic component result in relatively low heritabilities of 0.05 to 0.10 (Blasco et al., 1995; Van Arendonk et al., 1996; Rothschild and Bidanel, 1998), but the existence of large genetic variation offers opportunities for selection (Van Arendonk et al., 1996). The genetic component of pig survival consists of a maternal genetic component (genotype of the mother) and a direct genetic component (genotype of the pig). The maternal genetic component may influence pig survival through uterus quality and mothering ability and the direct genetic component may influence pig survival through the intrinsic vitality of the pig. This study was restricted to the direct genetic component of pig survival. Information on relationships of survival-related factors with the direct genetic component of pig survival will give insight into the biological background of genetic differences in pig survival. Approximately 80% of pig mortality occurs during birth and

within the first 3 d after birth (Svendsen, 1992), so we chose this period to study the biological backgrounds of genetic differences in pig survival.

The reported stillbirth rate (8.4% of total number of pigs born) in the present study is somewhat high, but is within the range of values (4 to 10%) that are reported in literature (reviewed by Cutler et al., 1992). The high stillbirth rate in this study may be due to the lower survival probability of purebred pigs compared to crossbred pigs (Blasco et al., 1995), or to the fact that none of the farrowings was assisted (Holyoake et al., 1995). The preweaning mortality rate (6.8% of total number of live-born pigs) within the first 3 d after birth in the present study is in agreement with values reported in the literature (Fahmy and Bernard, 1971; Bille et al., 1974).

Our results show that farrowing survival and early postnatal survival increased with increasing EBVps. This substantiates that part of the variation in pig survival can be explained by differences in genetic merit for pig survival. Next, we investigated whether these genetic differences in pig survival were related to differences in survival-related factors such as birth weight, birth intervals, duration of farrowing, early postnatal behavior, or rectal temperature.

Birth weight is considered to be one of the most important factors influencing pig survival. In general, farrowing survival and postnatal survival increase with increasing birth weight (Sharpe, 1966; Leenhouwers et al., 1999). In our study, these results were confirmed only for the relationship of early postnatal survival with individual birth weight. The lack of a significant relationship between farrowing survival and individual birth weight is in agreement with results from Zaleski and Hacker (1993). They found that average birth weight of the litter, rather than individual birth weight, was related to the probability of farrowing survival. To account for the effect of EBVps on farrowing and early postnatal survival, we analyzed whether birth weight was related to EBVps. Surprisingly, we found that birth weight significantly decreased with increasing EBVps. Thus, pigs with higher EBVps have an increased farrowing and early postnatal survival, despite their lower birth weight. When pigs with the largest difference in EBVps were compared at similar birth weights, it seemed that the difference in early postnatal survival was mainly seen in pigs weighing less than approximately 1.50 kg (Figure 2). This indicates that the genetic component of pig survival may be related to physiological characteristics that predominantly play a role in survival chances of lighter pigs. An example of such a physiological

characteristic is the amount of energy reserves (e.g., fat or glycogen) of a pig at birth (Randall and L'Ecuyer, 1976; Le Dividich et al., 1998).

The progress of farrowing plays an important role in farrowing survival and early postnatal survival. In general, farrowing survival decreases with a longer duration of farrowing and longer birth intervals, due to an increased risk of suffocation in the birth canal (Randall, 1972; Zaleski and Hacker, 1993). Oxygen stress experienced during birth also influences pig vitality and may therefore affect subsequent survival chances (Herpin et al., 1996). In our study, no relationship of farrowing survival to the progress of farrowing could be detected. We only found a relationship of early postnatal survival to the duration of farrowing. In this study, we also did not find a strong relationship between duration of farrowing or birth interval and EBVps. Unexpectedly, a tendency for increasing birth intervals with increasing EBVps was observed. Apparently, progress of farrowing is not strongly related to the genetic merit of the pig for survival. However, it is likely that predominantly genes of the sow influence the course of farrowing. In this case, the maternal genetic component of pig survival may be related to differences in the progress of farrowing.

Behavioral traits such as the time until first upright standing, the time until first udder contact, time until first teat in mouth and the time until first colostrum uptake are indicators of pig vitality and can predict pre-weaning survival (Junghans, 1992; Hoy et al., 1997). On average, pigs that show long time intervals for these indicators have lower survival chances. Rapid udder contact and subsequent colostrum uptake after birth are important for thermoregulation, maintenance of blood glucose levels, and acquiring antibodies (Curtis and Bourne, 1971; Le Dividich and Noblet, 1981; Herpin and Le Dividich, 1995). In this study, we found that shorter time intervals for the behavioral indicators are indeed related to increased survival chances. However, short time intervals for these indicators were not associated with high EBVps. On the contrary, the time until first teat in mouth became significantly longer as EBVps increased. Apparently, increased survival with increasing EBVps cannot be explained by differences in the studied postnatal behavior.

Newborn pigs are very susceptible to cold because of their low energy reserves, lack of brown adipose tissue, and poor insulation (Berthon et al., 1996). As a consequence of a low thermoregulatory capacity, pigs may become hypothermic. This is indicated by a below-average rectal temperature. Hypothermia impairs glucose metabolism and is associated with a reduced colostrum uptake, which of course has consequences for pig survival (Le Dividich

and Noblet, 1981; Close et al., 1985). In this study, no relationship between early postnatal survival and rectal temperature was found. Additionally, no relationship was found between EBVps and rectal temperature. This indicates that the direct genetic component of pig survival is not related to differences in rectal temperature. It cannot be excluded that EBVps is related to the ability to maintain body temperature under adverse conditions.

In conclusion, increased pig survival with increasing EBVps cannot be explained by progress of farrowing, early postnatal behavior, or rectal temperature within 24 h after birth.

Implications

Selection on the direct genetic component of pig survival will lead to lighter pigs at birth, that nevertheless survive better during farrowing and within the first 3 d after birth. Selection will not change the progress of farrowing or early postnatal pig behavior. Improved survival in relation to genetic merit for pig survival is mainly evident in smaller pigs. Information on the physiological state of pigs at the end of gestation in relation to their genetic merit for pig survival may provide more insights into the biological backgrounds of genetic differences in pig survival.

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Chapter 5

Fetal development in the pig in relation to genetic merit for piglet survival

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Abstract

The objective of this study was to investigate if litters with different genetic merit for piglet survival differ in late fetal development. In total, 507 fetuses from 46 litters were delivered by Caesarean section at, on average, d 111 of gestation. All litters had known estimated breeding values for piglet survival (EBVps). The obtained range of EBVps of the litters was continuous and the difference between litters with the lowest and highest EBVps was 16.4%. Analysis of relationships between fetal characteristics and EBVps was performed with litter averages, using linear regression analysis with inclusion of EBVps as a covariate. An increase in EBVps of the litter was associated with decreases in average placental weight ($P = 0.01$) and within-litter variation in placental weight ($P = 0.02$), and an increase in average placental efficiency ($P = 0.08$). Average fetal length decreased with increasing EBVps ($P = 0.04$), but weights of liver ($P = 0.02$), adrenals ($P = 0.0001$), and small intestine ($P = 0.01$) showed relative increases with increasing EBVps. Average serum cortisol concentrations very significantly increased with increasing EBVps ($P = 0.0001$), but the other blood characteristics (hematocrit, glucose, fructose, albumin, estradiol-17ß) were not related to EBVps. Glycogen concentrations in liver ($P = 0.07$) and longissimus dorsi muscle ($P = 0.04$), and total liver glycogen content ($P = 0.05$) increased with increasing EBVps, whereas heart glycogen concentration decreased with increasing EBVps ($P = 0.005$). The percentage of carcass fat increased with increasing EBVps ($P = 0.05$). Relationships of relative liver weight, relative small intestinal weight, and liver and muscle glycogen levels with EBVps were solely due to highly elevated serum cortisol levels in litters with high EBVps. The observed differences in fetal development in relation to EBVps suggest a higher degree of physiological maturity in litters with high EBVps. Differences in fetal cortisol accounted for most of these maturational differences. The results imply that selection for improved piglet survival will lead to slightly smaller piglets that nevertheless have an improved ability to cope with hazards during birth or within the first days of life.

Keywords: Pigs; Perinatal Mortality; Breeding Value; Animal Breeding; Placental Efficiency; Fetal Development.

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Introduction

Piglet survival can be increased by genetic selection on the basis of estimated breeding values for piglet survival (EBVps). Litters with high and low EBVps show marked differences in percentage stillbirth and mortality until weaning (Knol et al., 2001a). The increased survival rates of litters with high EBVps are not due to differences in the progress of parturition or early postnatal piglet behavior (Leenhouwers et al., 2001). Therefore, we hypothesized that the biological background of genetic differences in piglet survival might be found in differences in late fetal development that are related to the ability of piglets to adapt to the various changes associated with transition from intrauterine to extrauterine life. The degree of late fetal development and maturation is an important predisposing factor for stillbirth and preweaning mortality and involves characteristics like placental functioning, functional maturity of vital organs and availability of body energy reserves (Knight et al., 1977; Randall, 1992; reviewed by Van der Lende et al., 2001).

The objective of this study was to investigate if litters with different EBVps differ in fetal development at d 111 of gestation. Fetal development was characterized by body weight and length, placental characteristics, organ characteristics, blood characteristics, glycogen reserves, and body composition.

Material and Methods

Animals, Housing, and Feeding

This experiment was conducted strictly in line with the regulations of the Dutch law on the protection of animals. The gilts (n = 46) that were used in this study originated from a multiplier farm (Someren, The Netherlands) and were transported to the experimental accommodation 'De Haar' of Wageningen University, The Netherlands between the age of 11 and 20 weeks. Upon arrival at the experimental accommodation, gilts were housed in groups of five, according to body weight. After their arrival, all gilts were fed 0.9 to 1.5 kg/d of a starter diet (per kg: 13.8 MJ of ME; 167 g of CP; 10.0 g of lysine) until they reached the age of 15 weeks. Beyond this age, they received, depending on body condition, up to 2.3 kg/d of a rearing sow diet (per kg: 12.9 MJ of ME; 155 g of CP; 8.0 g of lysine). From the age of six months onwards, gilts were checked daily for estrus with a vasectomized boar. At second, third or fourth estrus, gilts were artificially inseminated twice on consecutive days with semen of one of 14 different boars. Gilts that returned to estrus after insemination were inseminated again. Three months after the start of estrus check, 7 gilts did not show a natural estrus. For these gilts, estrus was induced by administration of PG 600 (Intervet Nederland B.V., Boxmeer, The Netherlands). These gilts were inseminated at second estrus after induction. After insemination of the last gilt in a group of five, gilts were fed 2.3 kg/d of a special gestational diet (per kg: 12.2 MJ of ME; 140 g of CP; 7.0 g of lysine).

Experimental Design

All gilts were of the crossbred line D12 of TOPIGS breeding company (Vught, The Netherlands). Line D12 was produced by D2 dams mated by D1 sires. Line D1 was founded in 1968 and originates from different Piétrain populations. Since 1993, line D1 is selected mainly for litter size and piglet survival. Line D2 was founded in 1968 and originates from different Great Yorkshire and Large White populations. Since 1993, line D2 is selected on litter size and mothering ability. To inseminate the D12 dams, semen of boars of a sire line S of TOPIGS breeding company was used. Line S was founded in 1976, using selected animals from dam lines D1 and D2 to produce a specialized sire line. Line S was solely selected on growth, feed-intake, and backfat thickness until 1993, when piglet survival was added to the breeding goal.

For this experiment, gilts and boars were chosen on basis of their EBVps. Matings were done in such a way that a maximum contrast in EBVps of the litters was achieved. All fetuses within a litter had the same EBVps, calculated as the average of the respective gilt and boar. Estimated breeding values for piglet survival included survival from onset of farrowing until weaning and were calculated using an animal model, with direct (piglet) and nurse sow as animal effects. Heritabilities for the direct and nurse sow effects were 0.032 and 0.035, respectively, and the genetic correlation was 0.00. Piglet survival was defined as a binary trait, with a zero score for piglets dead before or at weaning, including stillborn piglets, and a score of 100 if alive at the day of weaning. Sex, birth weight of the piglets in classes of 100 gram, and litter size were taken as fixed effects, while litter effect of the natural mother of the piglets was taken as an uncorrelated random effect. The method for estimation of breeding values for piglet survival was described in more detail by Knol et al. (2001b). The obtained range of EBVps of the litters in this study was continuous and the difference between litters with the lowest and highest EBVps was 16.4%. This indicates an expected phenotypic difference in piglet survival from onset of farrowing until weaning of 16.4% between those litters.

Data Collection Procedures

In total, 507 fetuses from 46 litters were delivered by Caesarean section between d 110 and 112 of gestation. On the day of surgery, gilts were food-deprived, weighed and subsequently anaesthetized by i.m. injection of 20 mL Stresnil (Janssen Pharmaceutica N.V., Beerse, Belgium). Approximately one hour before surgery, i.m. injections of 3 mL of dormicum (Roche Nederland B.V., Mijdrecht, The Netherlands) and 9 mL of ketamine (Eurovet Animal Health B.V., Bladel, The Netherlands) were administered. Gilts were ear-catheterized (Microflex, Instruvet, Amerongen, The Netherlands) and additional i.v. injections of ketamine and dormicum were administered during surgery when necessary.

As each fetus was removed from the uterus, approximately 10 mL of blood was collected from the umbilical vein and umbilical artery via a 21-gauge needle (Terumo Europe N.V., Leuven, Belgium) and a 10-mL syringe (Terumo Europe N.V., Leuven, Belgium). In the smaller fetuses it was not always possible to collect 10 mL from both vessels. For every third fetus, starting with the first, samples of umbilical venous and arterial blood were immediately after collection analyzed for partial pressure of oxygen (pO_2) and carbondioxide (pCO_2) by the I-STAT handheld blood analyzer (I-STAT Corporation,

Princeton, USA). Measurement of pO_2 and pCO_2 was performed to ascertain that fetuses would not get hypoxic during the surgery procedure. Blood samples were collected into ice-cooled tubes without additive, with EDTA-NaF additive (i.e. a glycolysis inhibitor), and with lithium-heparin additive. Tubes were placed on ice and centrifuged at 2,000 × *g* for 10 min at 4 °C. Serum and plasma were stored at –20 °C until further analysis.

After blood collection, surgical silk (Instruvet B.V., Amerongen, The Netherlands) with a numbered tag was attached to the umbilical cord. The umbilical cord was then cut at 1 cm of the fetal abdomen, allowing the tagged cord to retract into the uterus. Each fetus was subsequently tagged with a matching number, thus allowing individual matching of fetus and placenta. After the umbilical cord was cut, fetuses were euthanatized immediately by intracardial injection of 0.5 mL of a mixture of a central nervous system narcotic, a paralytic agent, and a local anaesthetic (T-61, Hoechst Roussel Vet N.V., Brussels, Belgium).

Directly following euthanasia, fetuses were weighed and samples of heart (apex of cardiac ventricles), liver, and muscles including the longissimus dorsi (LD) and the biceps femoris (BF) muscles were collected. These samples were immediately frozen by immersion in liquid nitrogen and then stored at -80 °C until they were analyzed for glycogen content. Heart and liver glycogen were determined for all individual fetuses. Based on average fetal body weight of the litter, two average fetuses were selected for analysis of muscle glycogen. These fetuses were also used for analysis of carcass moisture, protein, fat, and ash content. After surgery, fetal crown-rump length was determined and the remaining internal organs (lungs, stomach, spleen, kidneys, adrenals, and small intestine) were removed and individually weighed. Length of the small intestine was also measured.

After surgery, the gilt was euthanatized by i.v. administration of a lethal dose of T-61. Next, the uterus was removed and the uterine horns were opened longitudinally along the anti-mesometrial side. Placentae were collected by carefully detaching them from the endometrium. The umbilical cord was cut from each placenta at the point where the umbilical arteries diverge and subsequently cord length was measured. After removal of the umbilical cords, placentae were individually weighed and their length was measured. Placental efficiency was calculated as the ratio fetal body weight: placental weight.

Chemical Analytical Procedures

To determine hematocrit values, freshly collected blood was spun down in capillaries in a hematocrit centrifuge at 11,330 × *g*. Venous and arterial plasma glucose concentrations

were determined spectrophotometrically in triplicate with the glucose oxidase-peroxidase anti-oxidase method, using a commercial kit (GOD-PAP, Boehringer, Mannheim, Germany). Arterial plasma fructose concentrations were determined by radial immunodiffusion, as described by Roe (1934). Arterial plasma albumin concentrations were determined by RIA using a commercial kit (CEA, Gif, France). Arterial serum cortisol concentrations were determined by a solid-phase ^{125}I RIA method (Coat-A-Count TKCO; Diagnostic Products Corporation) according to the description of the manufacturer. The limit of quantitation was 16 nmol/l and the interassay coefficient of variation was 7.3 % (n=7). Arterial serum estradiol-17ß concentrations were estimated by a solid-phase ^{125}I RIA method (Coat-A-Count TKE; Diagnostic Products Corporation, Los Angeles, CA, U.S.A.) according to the description of the manufacturer with slight modifications as described for the cow (Dieleman and Bevers, 1987). The limit of quantitation was 35 pmol/L and the interassay coefficient of variation was 13.3 % (n = 7).

Glycogen concentrations in heart, liver, and muscle were determined by the method of Carroll et al. (1956). Glycogen was extracted from the tissue by homogenization with 5% trichloroacetic acid solution. Glycogen was precipitated from the extract by 95% ethanol and determined with anthrone reagent in a colorimeter at 620 nm.

For analysis of body composition, frozen carcasses were weighed, cut into pieces, and homogenized separately in a commercial butcher's mincer. The homogenates were stored at –20 °C in sealed plastic bags until they were analyzed in duplo for moisture, protein, fat, and ash content. Moisture content was determined gravimetrically, after drying at 103 °C for 4 h. Nitrogen content (N) was measured using the Kjeldahl method, and protein values were calculated as N × 6.28. Fat content was determined by petroleum-ether extraction. Ash was determined gravimetrically after incineration at 550 °C for 3 h.

Statistical Analysis

Stage of gestation at fetus removal (GL) was calculated as the difference between day of Caesarean section and day of second insemination. Mummified fetuses were excluded from all analyses. Non-fresh dead fetuses at the moment of Caesarean section were included in the calculation of total number of fetuses (TNF) and average fetal body weight (ABW), but excluded from all other characteristics. Litter averages and within-litter standard deviation were calculated for all characteristics. Litter averages for body composition and muscle

glycogen concentrations were calculated on basis of the two fetuses per litter that were analyzed for these traits.

All data were analyzed using the GLM procedure of SAS (SAS Inst. Inc., Cary, NC). The following models were used to analyze relationships of body and placental characteristics (model 1.1), and blood characteristics, glycogen reserves, and body composition (model 1.2) with EBVps:

$$Y_{ij} = \mu + GL_i + b_1M + b_2TNF + b_3EBVps + e_{ij}, \quad (1.1)$$

$$Y_{ij} = \mu + GL_i + b_1M + b_2TNF + b_3EBVps + b_4ABW + e_{ij}, \quad (1.2)$$

where Y_{ij} is the dependent variable; μ = overall mean; GL_i = stage of gestation (i = 110-112); M = percentage males within the litter; TNF = total number of fetuses; EBVps = estimated breeding value for piglet survival of the litter; and e_{ij} = residual error. The effect of EBVps was tested against the residual error term. Stepwise elimination of non-significant (co)variates ($P > 0.05$) was applied.

The following models were used to analyze relationships of relative liver and small intestinal weights (model 2.1) and glycogen reserves (model 2.2) with serum cortisol concentrations:

$$Y_{ij} = \mu + GL_i + b_1C + b_2C^2 + e_{ij}, \quad (2.1)$$

$$Y_{ij} = \mu + GL_i + b_1C + b_2C^2 + b_3ABW + e_{ij}, \quad (2.2)$$

where Y_{ij} = dependent variable; μ = overall mean; GL_i = stage of gestation (i = 110-112); C = serum cortisol concentration; C^2 = quadratic cortisol term; and e_{ij} = residual error. The quadratic cortisol term was removed from the model in case of non-significance ($P > 0.10$).

The relationship between organ weight (Y) and fetal body weight (BW) can be described by the following power function (Huxley, 1924):

$$Y = aBW^b, \quad (3)$$

where a = the proportionality coefficient (the intercept at unity); and b = scaling coefficient.

To investigate relationships of organ characteristics (organ weights and length of the small intestine) with EBVps, Eq. (3) was extended into Eq. (4):

$$Y = a' e^{b_1 EBVps} BW^{(b_2 + b_3 EBVps)} \qquad (4)$$

Equation (4) was transformed into a linear form by taking the natural logarithm:

$$\ln(Y) = \ln(a') + b_1 EBVps + b_2 \ln(BW) + b_3 EBVps \times \ln(BW). \qquad (5)$$

Parameter estimates and *P*-values for b_1, b_2, and b_3 were obtained from Eq. (5) by the GLM procedure. The individual fetus was used as the experimental unit and effects of EBVps, ln(BW), and the EBVps × ln(BW) interaction were tested against sow as an error term. The interaction EBVps × ln(BW) was nonsignificant ($P > 0.10$) for all organs and subsequently removed from the model. This resulted in the following model (6) that was used to analyze relationships of organ characteristics with EBVps:

$$\ln(Y_{ijk}) = \mu + GL_i + b_1 EBVps + b_2 \ln(BW) + Sow_j + e_{ijk}, \qquad (6)$$

where Y_{ijk} = dependent variable; μ = overall mean; GL_i = stage of gestation (i = 110-112); EBVps = estimated breeding value for piglet survival of the litter; BW = individual fetal body weight; Sow_j = sow effect (j = 1-46); and e_{ijk} = residual error. The effects of EBVps and ln(BW) were tested against Sow_j as an error term. GL_i was removed from the model if non-significant ($P > 0.05$).

For comparison of fetal characteristics between litters with low, average, or high EBVps, litters were divided into three classes on basis of their EBVps. Least-squares means per EBVps class were computed by the LSMEANS statement in Proc GLM in a model which only included stage of gestation as a fixed effect. Significant differences between least-squares means were tested by inclusion of the PDIFF option in the LSMEANS statement.

Results

General

The average stage of gestation in this experiment was 111.1 d (SD = 0.8 d). The total number of fetuses per litter averaged 11.0 (SD = 2.8 fetuses), which included 0.1 non-fresh dead fetuses (SD = 0.3 fetuses). Venous blood pO_2 and arterial blood pCO_2 values were measured for every third fetus during Caesarean section. On average, concentrations of venous O_2 and arterial CO_2 remained constant during the surgery procedure (Figure 1).

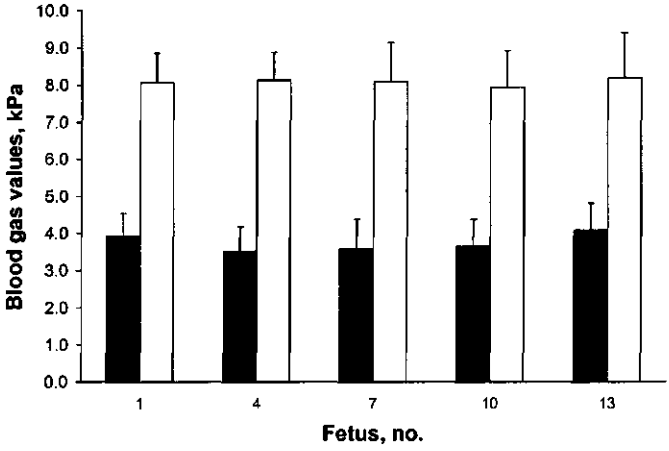

Figure 1. Average venous blood pO_2 (■) and arterial blood pCO_2 (□) values measured for every third fetus during Caesarean section.

Relationships with EBVps

Body and Placental Characteristics

Relationships of body and placental characteristics with EBVps are presented in Table 1. Average body length decreased with increasing EBVps, whereas average body weight was not related to EBVps. Fetuses of litters with high EBVps (mean EBVps = +7.9%) were on average 1.3 cm shorter than fetuses of litters with low EBVps (mean EBVps = -3.8%). Within-litter variation in body weight and length were not related to EBVps. Average placental weight showed a decrease with increasing EBVps. Placentae of litters with high

Table 1. Relationships of body and placental characteristics with EBVps of the litter[a]

Characteristic[b]	n[c]	Litter average			Within-litter variation[e]		
		Mean ± SE	Regression coefficient[d]	*P*-value	Mean ± SE	Regression coefficient[d]	*P*-value
Body wt, g	46	1155 ± 26	-7.70	0.12	188 ± 9	0.37	0.84
Body length, cm	46	29.0 ± 0.2	-0.08	0.04	1.6 ± 0.08	-0.004	0.80
Placental wt, g	45	214.1 ± 6.4	-2.99	0.01	48.6 ± 2.5	-1.10	0.02
Placental length, cm	45	62.3 ± 1.8	-0.55	0.12	8.7 ± 0.6	-0.04	0.73
Placental efficiency, (g/g)	45	5.6 ± 0.1	0.04	0.08	0.8 ± 0.03	-0.006	0.37
Umbilical cord length, cm	46	25.0 ± 0.4	-0.04	0.62	3.8 ± 0.2	-0.04	0.29

[a]EBVps = estimated breeding value for piglet survival.

[b]Placental efficiency was calculated as ratio body weight: placental weight.

[c]Number of litters.

[d]Regression coefficients indicate the increase or decrease in the respective characteristic with every percentage increase in EBVps.

[e]Calculated as within-litter standard deviation.

EBVps (mean EBVps = +7.9%) were on average 40 g lighter than placentae of litters with low EBVps (mean EBVps = -3.8%). Within-litter variation in placental weight also decreased with increasing EBVps. Placental efficiency tended to increase with increasing EBVps. Average umbilical cord length and within-litter variation in umbilical cord length were not related to EBVps.

Organ Characteristics

Absolute and relative values of organ characteristics for all litters and for three EBVps classes are shown in Table 2. With the exception of adrenal weight, absolute values of organ characteristics tended to be lower in litters with high EBVps. Litters with high EBVps had higher relative weights of liver and adrenals, and relatively longer small intestines, but relatively lighter spleens than litters with low EBVps.

Relationships of organ characteristics with EBVps were calculated taking into account the existence of allometric relationships between organ characteristics and body weight (Table 3). The 95%-confidence intervals for the values of b_2 show a significant deviance from 1.0 for stomach weight, kidney weight, adrenal weight, and small intestinal length, thus indicating non-isometric relationships between these organ characteristics and body weight. Significant positive estimates of b_1 for weights of liver, adrenals, and small intestine indicate relative increases in these organ weights with increasing EBVps. Stomach weight tended to show a relative increase with increasing EBVps, whereas spleen weight tended to show a relative decrease with increasing EBVps. These values for b_1 indicate that the liver, adrenals, small intestine, and stomach of a fetus with an EBVps of +5% will be 7.1%, 21.7%, 5.4%, and 4.3% heavier, respectively, than those of a fetus of the same weight but with an EBVps of –5%. In contrast, the spleen will weigh 6.1% less.

Table 2. Absolute and relative values of organ characteristics for all litters and for three EBVps classes[a]

	Absolute value				Relative value[c]			
		EBVps class[b]				EBVps class[b]		
Characteristic	All litters (n = 46)	Low (n = 16)	Average (n = 15)	High (n = 15)	All litters (n = 46)	Low (n = 16)	Average (n = 15)	High (n = 15)
Heart wt, g	10.1 ± 0.3	10.8 ± 0.4^{x}	10.1 ± 0.4^{xy}	9.3 ± 0.4^{y}	8.7 ± 0.1	8.9 ± 0.1	8.7 ± 0.1	8.6 ± 0.1
Liver wt, g	33.2 ± 0.8	33.9 ± 1.4	32.2 ± 1.4	32.9 ± 1.4	28.6 ± 0.5	27.9 ± 0.7^{x}	27.5 ± 0.7^{x}	30.2 ± 0.7^{y}
Lung wt, g	40.4 ± 1.1	43.1 ± 1.9^{x}	40.0 ± 1.9^{xy}	37.3 ± 2.0^{y}	34.8 ± 0.5	35.4 ± 0.9	34.3 ± 0.9	34.3 ± 0.9
Stomach wt, g	6.0 ± 0.1	6.1 ± 0.2	6.2 ± 0.2	5.7 ± 0.2	5.2 ± 0.1	5.0 ± 0.1	5.4 ± 0.1	5.2 ± 0.1
Spleen wt, g	1.3 ± 0.04	1.3 ± 0.07^{x}	1.4 ± 0.07^{x}	1.0 ± 0.07^{y}	1.1 ± 0.02	1.1 ± 0.04^{x}	1.2 ± 0.04^{x}	1.0 ± 0.04^{y}
Kidney wt, g	7.7 ± 0.2	8.1 ± 0.3^{x}	8.1 ± 0.3^{x}	7.1 ± 0.3^{y}	6.7 ± 0.1	6.7 ± 0.1	6.9 ± 0.1	6.6 ± 0.1
Adrenal wt, g	0.142 ± 0.004	0.125 ± 0.005^{x}	0.143 ± 0.005^{y}	0.151 ± 0.005^{y}	0.125 ± 0.004	0.105 ± 0.005^{x}	0.125 ± 0.005^{y}	0.140 ± 0.005^{z}
Small intestinal wt, g	28.1 ± 0.8	28.7 ± 1.3	28.9 ± 1.3	26.7 ± 1.3	24.2 ± 0.3	23.7 ± 0.5	24.6 ± 0.5	24.5 ± 0.5
Small intestinal length, cm	326 ± 4	325 ± 8	330 ± 8	320 ± 8	290 ± 5	278 ± 8^{x}	290 ± 8^{xy}	301 ± 8^{y}

[a]EBVps = estimated breeding value for piglet survival.

[b]Mean EBVps class low: –3.8%; average: +2.0%; high: +7.9%.

[c]Relative values are expressed per kg body weight and were calculated for each individual fetus and subsequently averaged per litter.

[x,y,z]Columns with different superscripts are significantly different at $P < 0.05$.

Table 3. Regression coefficients and *P*-values for the model: $\ln(Y) = \ln(a') + b_1EBVps + b_2\ln(BW)$[a]

		EBVps		ln(BW)	
Y	ln(a')	Regression coefficient[b]	*P*-value	Regression coefficient[b]	95% C.I.[c]
Heart wt, g	-4.47	-0.0025	0.15	0.96	0.92-1.00
Liver wt, g	-3.32	0.0069	0.02	0.97	0.92-1.02
Lung wt, g	-3.30	-0.0031	0.30	0.99	0.92-1.06
Stomach wt, g	-4.14	0.0042	0.09	0.84	0.79-0.89
Spleen wt, g	-6.81	-0.0063	0.10	0.99	0.92-1.07
Kidney wt, g	-3.93	-0.0008	0.73	0.85	0.80-0.90
Adrenal wt, g	-5.80	0.0196	0.0001	0.55	0.47-0.63
Small intestinal wt, g	-4.02	0.0053	0.01	1.04	1.00-1.09
Small intestinal length, cm	2.88	0.0015	0.44	0.41	0.37-0.45

[a]Y = organ characteristic; ln(a') = intercept; EBVps = estimated breeding value for piglet survival; BW = body weight; b_1, b_2 = regression coefficients. [b]Regression coefficients indicate the increase or decrease in the natural logarithm of the respective characteristic with every percentage increase in EBVps.[c]95%-confidence interval was calculated as the regression coefficient ± 1.96*SE of the regression coefficient.

Blood Characteristics

Average serum cortisol concentrations increased with increasing EBVps, whereas within-litter variation in cortisol levels was not related to EBVps (Table 4). Average serum cortisol levels and adrenal weights for litters with low, average, and high EBVps are shown in Figure 2. No relationships were found between other blood characteristics and EBVps.

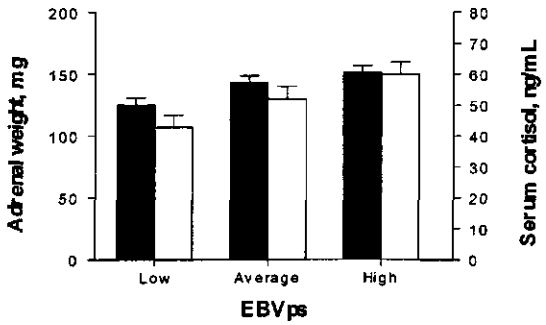

Figure 2. Average adrenal weights (■) and serum cortisol levels (□) for litters with low (mean EBVps = -3.8%), average (mean EBVps = +2.0%), and high EBVps (mean EBVps = +7.9%).

Table 4. Relationships of blood characteristics with EBVps of the litter[a]

Characteristic	n[b]	Litter average			Within-litter variation[d]		
		Mean ± SE	Regression coefficient[c]	*P*-value	Mean ± SE	Regression coefficient[c]	*P*-value
Hematocrit, %	38	30.4 ± 0.5	0.08	0.41	2.5 ± 0.2	0.06	0.12
Plasma venous glucose, mg/100 mL	46	62.6 ± 1.4	0.14	0.62	8.5 ± 0.5	-0.03	0.75
Plasma arterial glucose, mg/100 mL	46	55.0 ± 1.4	0.11	0.70	9.7 ± 0.6	-0.03	0.77
Plasma arterial fructose, mmol/L	46	3.19 ± 0.10	-0.01	0.51	0.51 ± 0.02	0.002	0.65
Plasma arterial albumin, g/L	46	6.83 ± 0.14	0.04	0.16	1.03 ± 0.06	0.001	0.92
Serum arterial estradiol-17ß, ng/mL	46	1.42 ± 0.09	-0.01	0.51	0.56 ± 0.04	-0.003	0.71
Serum arterial cortisol, ng/mL	46	51.5 ± 2.6	1.7	0.0001	15.3 ± 1.3	0.2	0.53

[a]EBVps = estimated breeding value for piglet survival.

[b]Number of litters.

[c]Regression coefficients indicate the increase or decrease in the respective characteristic with every percentage increase in EBVps.

[d]Calculated as within-litter standard deviation.

Glycogen Reserves and Body Composition

Regression coefficients and *P*-values of relationships of glycogen reserves and body composition with EBVps are presented in Table 5. Average total liver glycogen content and LD muscle glycogen concentration increased with increasing EBVps, whereas heart glycogen concentration decreased with increasing EBVps. Total liver glycogen content and LD muscle glycogen concentration of fetuses from litters with high EBVps (mean EBVps = +7.9%) were 8.1% and 6.2% higher, respectively, than of fetuses from litters with low EBVps (mean EBVps = -3.8%). Heart glycogen concentrations were 9.6% lower in fetuses from litters with high EBVps. Liver glycogen concentration tended to increase with increasing EBVps and the glycogen concentration in BF muscle was not related to EBVps.

Liver glycogen concentrations were positively correlated with LD muscle ($r = 0.42$, $P < 0.0001$) and BF muscle ($r = 0.41$, $P < 0.0001$) glycogen concentrations. There was an overall positive correlation between glycogen concentrations in the two muscle types ($r = +0.60$, $P < 0.0001$). Heart glycogen concentrations were not correlated with glycogen concentrations in liver, LD muscle, and BF muscle ($P > 0.10$).

The average fat percentage of the carcasses increased with increasing EBVps. No relationships with EBVps were found for moisture, protein, and ash content of the carcasses.

Relationships with Cortisol

Small Intestinal Weight and Liver Weight

Relative small intestinal and liver weight both increased with increasing serum cortisol levels (Table 6). After subtracting the total amount of liver glycogen from the liver weight, the residual relative liver weight was also positively related to serum cortisol. After accounting for effects of cortisol, there were no additional effects of EBVps on these organ weights ($P > 0.10$). Thus, effects of EBVps on liver and small intestinal weights (see Table 3) were solely due to cortisol differences.

Glycogen Reserves

Glycogen concentrations in liver, LD muscle, and BF muscle increased with increasing serum cortisol concentrations, as did the total amount of liver glycogen. No additional effects of EBVps on liver and muscle glycogen levels were found after accounting for differences in serum cortisol ($P > 0.10$). Figure 3 shows that, in general, the higher serum

Table 5. Relationships of glycogen reserves and body composition with EBVps of the litter[a]

		Litter average[d]			Within-litter variation[f]		
Characteristic[b]	n[c]	Mean ± SE	Regression coefficient[e]	*P*-value	Mean ± SE	Regression coefficient[e]	*P*-value
Heart glycogen concentration, mg/g	46	15.6 ± 0.3	-0.13	0.005	2.1 ± 0.09	-0.009	0.58
Liver glycogen concentration, mg/g	46	101.8 ± 2.7	0.89	0.07	15.5 ± 0.7	0.05	0.69
Liver glycogen total, g	46	3.45 ± 0.15	0.05	0.05	0.89 ± 0.04	0.002	0.77
Muscle (LD) glycogen concentration, mg/g	46	70.9 ± 1.1	0.39	0.04	NC	NC	NC
Muscle (BF) glycogen concentration, mg/g	46	78.5 ± 1.3	0.33	0.17	NC	NC	NC
Carcass moisture, %	46	81.5 ± 0.1	-0.03	0.17	NC	NC	NC
Carcass protein, %	46	10.4 ± 0.1	0.003	0.82	NC	NC	NC
Carcass fat, %	46	0.72 ± 0.01	0.004	0.05	NC	NC	NC
Carcass ash, %	46	3.9 ± 0.1	-0.003	0.74	NC	NC	NC

[a]EBVps = estimated breeding value for piglet survival.

[b]LD = longissimus dorsi; BF = biceps femoris.

[c]Number of litters.

[d]Litter averages of LD and BF muscle glycogen concentrations and body composition traits are based on two fetuses per litter.

[e]Regression coefficients indicate the increase or decrease in the respective characteristic with every percentage increase in EBVps.

[f]Calculated as within-litter standard deviation.

[NC]Relationships between within-litter variation of these characteristics and EBVps were not calculated, because litter averages of these characteristics were based on two fetuses per litter.

Table 6. Relationships of relative small intestinal and liver weights and glycogen reserves with cortisol

Characteristic[a]	Cortisol		Cortisol^2	
	Regression coefficient[b]	*P*-value	Regression coefficient[b]	*P*-value
Relative small intestinal weight, g/kg body weight	0.26	0.0006	-0.002	0.003
Relative liver weight, g/kg body weight	0.09	0.0004	RM	
Residual relative liver weight, g/kg body weight	0.07	0.0005	RM	
Heart glycogen concentration, mg/g	-0.03	0.08	RM	
Liver glycogen concentration, mg/g	0.43	0.004	RM	
Liver glycogen total, g	0.02	0.002	RM	
Muscle (LD) glycogen concentration, mg/g	0.93	0.001	-0.007	0.004
Muscle (BF) glycogen concentration, mg/g	0.18	0.02	RM	

[a]Residual liver weight was calculated as liver weight minus glycogen content; LD = longissimus dorsi; BF = biceps femoris; Muscle glycogen concentrations were determined for two fetuses per litter. [b]Regression coefficients indicate the increase or decrease in the respective characteristic with every ng/mL increase in serum cortisol. [RM]Removed from the Model: the quadratic term Cortisol^2 was removed in case of non-significance ($P > 0.10$).

cortisol levels of fetuses with high EBVps (mean EBVps = +7.9%) compared to fetuses with low EBVps (mean EBVps = -3.9%) were associated with higher liver glycogen concentrations. Some fetuses exhibited very high cortisol levels that were not associated with high liver glycogen concentrations. Heart glycogen concentration decreased with increasing serum cortisol levels. However, cortisol had no additional effects ($P > 0.10$) other than its effect through the relationship with EBVps.

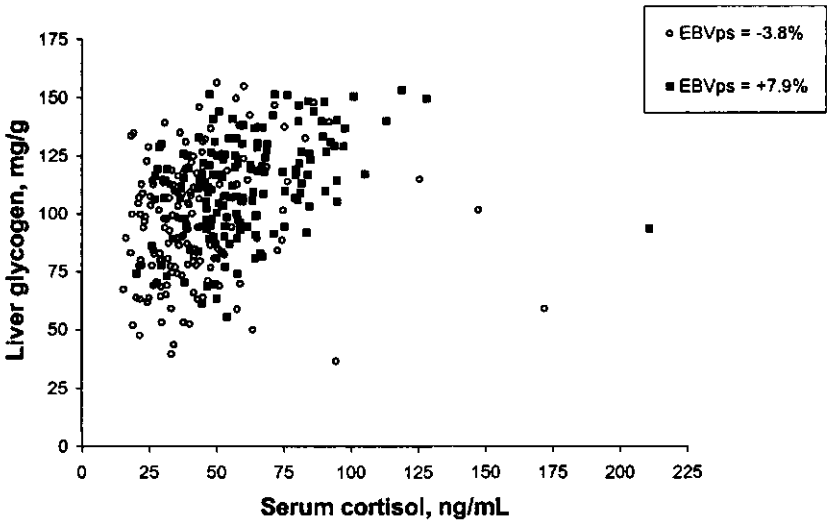

Figure 3. Relationship between liver glycogen concentration and serum cortisol for fetuses (n = 159) with high estimated breeding values for piglet survival (mean EBVps = +7.9%) and fetuses (n = 165) with low estimated breeding values for piglet survival (mean EBVps: -3.8%).

Discussion

The perinatal survival chances of a piglet mainly depend on its ability to cope with stresses experienced during farrowing and during the first days after birth (Pomeroy, 1960; Randall, 1978). This ability is not only influenced by environmental conditions, but also has a genetic component (reviewed by Rothschild and Bidanel, 1998; Knol, 2001). The survival chances of a piglet are influenced by its own genotype and by the genotype of the sow. Estimations of the direct genetic component of piglet survival were obtained by calculation of estimated breeding values for piglet survival (EBVps), which predict survival from onset of farrowing until weaning (Knol et al., 2001a). The present study reports results of late fetal development in relation to genetic merit for piglet survival of the litter.

Between d 90 and 110 of gestation, the fetus itself may be responsible for the increase in maternal-fetal nutrient exchange (Biensen et al., 1998). Increased fetal nutrient uptake is accomplished either by enlarging placental surface area or by increasing placental vascularity. In this study, the observed decreased placental weight, similar placental length,

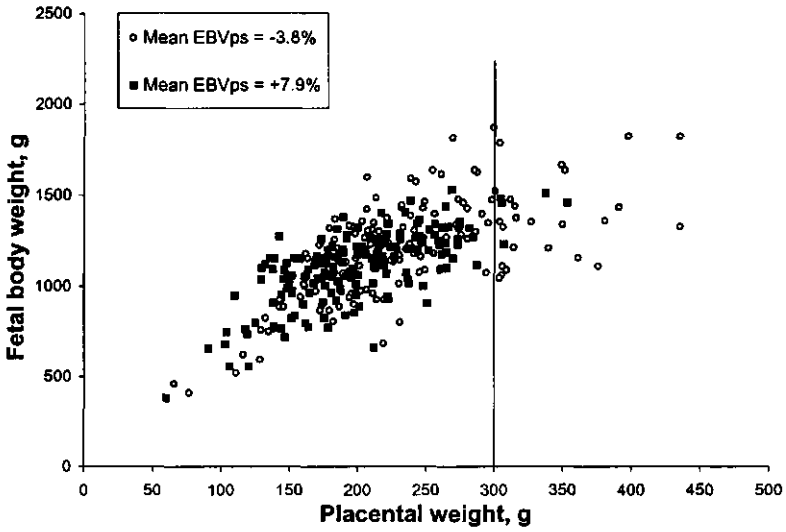

Figure 4. Relationship between fetal body weight and placental weight for fetuses (n = 163) with high estimated breeding values for piglet survival (mean EBVps: +7.9%) and fetuses (n = 160) with low estimated breeding values for piglet survival (mean EBVps: -3.8%). The vertical line at a placental weight of 300 g indicates the approximate point where fetal body weight does not increase anymore with increasing placental weight.

and increased placental efficiency with increasing EBVps suggest that fetuses with high EBVps employ the latter strategy. Variation in placental weight significantly decreased with increasing EBVps of the litter. Surprisingly, this decrease in variation in placental weight was not accompanied by a significant decrease in variation in fetal body weight. This result can be explained by the absence of very heavy placentae in litters with high EBVps. Beyond a certain placental weight, fetal weight does not increase anymore, indicating that a maximum fetal growth potential has been reached (Van Rens and Van der Lende, 2001). In this study, this stage is reached at a placental weight of approximately 300 g (Figure 4). Placentae heavier than 300 g occurred mainly in litters with low EBVps, thereby inducing extra variation in placental weight that was not accompanied by extra variation in fetal body weight.

The negative trend of the relationship between fetal body weight and EBVps and the significant decrease in fetal length with increasing EBVps indicate a trend for reduced piglet size with increasing EBVps. Reduced piglet size with increasing genetic merit for piglet

survival might seem contradictory in terms of piglet survival, because low birth weight reduces both farrowing and preweaning survival chances (Sharpe, 1966; English and Wilkinson, 1982). However, birth weight is not the sole important determining factor for piglet survival. In our own previous study we reported that piglets with a higher genetic merit for survival have lower birth weights, but increased survival chances during farrowing and within the first 3 d after birth (Leenhouwers et al., 2001). Meishan piglets have lower birth weights than Western breeds, but for their birth weight they have a greater ability to survive (Lee and Haley, 1995). Piglets from obese selection lines have lower birth weights than piglets from lean lines, but nevertheless 17% higher survival rates from birth to weaning (Mersmann et al., 1984). Explanations for the higher survival rates of obese compared to lean piglets could be a greater physiological maturity at birth, as suggested by differences in body and tissue composition, metabolic and hormonal state, and fat metabolism (Mersmann, 1984; Stone, 1984; Herpin et al., 1993). The current observed differences in organ weights (liver, adrenals, and small intestine), serum cortisol levels, glycogen reserves, and carcass fat percentage also suggest a higher degree of physiological maturity in litters with high EBVps.

Relative liver weight and liver glycogen content both increased with increasing EBVps. Liver glycogen plays an important role in glucose and thermal homeostasis in the period before ingestion of adequate amounts of colostrum (Mersmann, 1974). The prepartum rise in fetal cortisol levels (Kattesh et al., 1997) stimulates liver glycogen deposition, probably as a result of activation of glycogen synthetase (Schwartz and Rall, 1973; Fowden et al., 1985; Randall, 1988). Our findings confirm the stimulative effects of cortisol on glycogen deposition and show that relationships of relative liver weight and liver glycogen content with EBVps were solely due to EBVps-related differences in cortisol concentrations. Moreover, relative liver weight minus the liver glycogen content still showed a relationship with cortisol. As previously suggested by Randall (1989), this may indicate that effects of cortisol on the liver are not limited to stimulation of glycogen synthesis, but may also include influences on hepatocyte proliferation or hemopoietic tissue formation.

By the end of gestation, approximately 90% of all body glycogen can be found in skeletal muscle (Okai et al., 1978). Muscle glycogen reserves are important for thermogenesis, especially in the period before colostrum ingestion (McCance and Widdowson, 1959; Le Dividich et al., 1998). Glycogen concentration in the longissimus dorsi (LD) muscle increased with increasing EBVps, but no such relationship was found for the biceps femoris

(BF) muscle. Relationships between LD muscle glycogen concentrations and EBVps could be attributed to differences in cortisol concentrations. The positive relationship between muscle glycogen concentrations and cortisol is in agreement with results of Fowden et al. (1985). The effect of cortisol on BF glycogen concentration was, although significant, less clear. Randall (1988) also did not find a very strong effect of cortisol infusion on glycogen concentration in this muscle type, suggesting that other hormonal factors (e.g. insulin) may also play a role (Garssen et al., 1983).

In the fetal pig, heart glycogen concentrations remain fairly constant from d 60 of gestation until term (Randall and L'Ecuyer, 1976). Heart glycogen is thought to be related to the ability of fetal pigs, lambs, newborn rats, rabbits, and guinea-pigs to withstand asphyxia (Dawes et al, 1959; Randall, 1979). Therefore, the observed decrease in heart glycogen levels with increasing EBVps was rather unexpected. Explanations for this relationship are unknown at this time. Our current findings that heart glycogen concentrations are not related to circulating fetal cortisol levels are in agreement with other studies (Fowden et al., 1985; Randall, 1987).

Increased relative small intestinal weight with increasing EBVps could also be explained by variation in fetal cortisol levels. The effects of cortisol on the gastrointestinal tract (GIT) have been reviewed by Sangild et al. (2000). Cortisol prepares the GIT for the shift from parenteral nutrition before birth to enteral nutrition after birth. Effects of cortisol include enhanced GIT growth and structure, stimulation of GIT disaccharidase and peptidase enzyme activities, and stimulation of GIT immunoglobulin uptake. Together with increased serum cortisol levels, the increased relative small intestinal weight and tendency for increased stomach weight with increasing EBVps may indicate a higher degree of gastrointestinal development in litters with high EBVps. In this respect it is interesting to note that Knol et al. (2001c) found a positive genetic correlation between postnatal weight gain (g/d) measured between 29 and 130 kg BW and the direct genetic effect for pre-weaning piglet survival.

Knol et al. (2001c) also reported a significant positive genetic correlation between the direct genetic effect of preweaning survival and backfat measured at a BW range of 29 to 130 kg. Therefore, they concluded that selection for increased piglet survival will increase backfat. Our current results show that EBVps-related differences in body fat are already apparent at the end of gestation. Although the fetal carcass fat percentage was low (0.72%), and mobilization of body fat reserves during starvation is supposedly very low (reviewed by

Herpin and Le Dividich, 1995), body fat may play a role in preventing heat loss by increasing thermal insulation (Mount, 1964). Our results indicate a 0.0004% increase in carcass fat per 1% increase in EBVps, which corresponds to a relative increase of 9% in carcass fat between litters with the lowest (-5.91%) and highest (+10.47%) EBVps. This increase in carcass fat percentage possibly contributes to a better thermal insulation and thus may prevent heat loss in litters with high EBVps.

The adrenal of the fetal pig is very mature near the end of gestation and appears to be capable of responding to fetal distress (Lohse and First, 1981; Fowden et al., 1985). The very high cortisol levels in some of the fetuses (see Figure 3) most likely reflected a situation of fetal distress or disturbed fetal development. Closer examination of these fetuses learned that they either had low body weights, an enlarged heart, or that they were strangled by their own umbilical cord.

In conclusion, the observed relationships between characteristics of late fetal development and EBVps suggest an increase in physiological maturity with increasing EBVps. Higher physiological maturity in litters with high EBVps was likely due to the higher average cortisol concentrations in these litters. Whether the increased cortisol levels in litters with high EBVps are the result of increased ACTH levels produced by the pituitary or increased sensitivity of the adrenals to ACTH is currently unknown, but will be investigated in future experiments.

Implications

An increase in genetic merit for piglet survival is associated with changes in late fetal development which are probably due to differences in circulating fetal cortisol levels. Knowing that cortisol plays a major role in the preparation for the transition from intrauterine to extrauterine life, piglets with a higher genetic merit for piglet survival may have an improved ability to cope with hazards during birth and within the first days of life. The physiological pathways leading to increased cortisol levels in litters with high genetic merit for piglet survival and consequences of genetic selection for specific development of liver, small intestines and lungs will be investigated in future experiments.

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Chapter 6

General Discussion

Introduction

This Chapter consists of six sections. In the first section (6.1), the usefulness of estimated breeding values for piglet survival to study the biological background of genetic differences will be evaluated. In section 6.2, the results of Chapters 2 to 5 will be combined to summarize our current understanding of the biological mechanisms underlying genetic differences in survival. Results in this thesis suggest alterations of the hypothalamus-pituitary-adrenal axis (HPA axis) as a consequence of selection for piglet survival. Section 6.3 is meant to provide background information on the function and development of the HPA axis during late gestation in several species, with special emphasis on the pig. Knol (2001) mentions in his thesis the existence of striking resemblances between Meishan piglets and piglets of Western breeds with a high genetic merit for survival. Section 6.4 further discusses similarities between Meishan piglets and piglets with high genetic merit for survival on the basis of results presented in this thesis. In addition, similarities between piglets of genetically obese lines and piglets with a high genetic merit for survival will be discussed. Some examples on how the results of this thesis contribute to a better understanding of the consequences of selection are given in section 6.5. Furthermore, section 6.5 discusses possibilities for implementation of current results in the field. Finally, section 6.6 sums up general conclusions.

6.1. Usefulness of Estimated Breeding Values for Piglet Survival to Study Biological Backgrounds of Genetic Differences in Piglet Survival

Various studies have concluded that improvement of piglet survival by genetic selection is not efficient due to a large environmental variation on this trait and low heritabilities of 0.05 to 0.10 (reviewed by Blasco et al., 1995; Rothschild and Bidanel, 1998). However, estimation of genetic merit for piglet survival on the basis of large numbers of observations leads to estimated breeding values for piglet survival (EBVps) which have a good predictive value for realized survival. For instance, Knol (2001) used information of 60,000 piglets to estimate EBVps of future litters of gestating sows. He reported that realized survival of those litters corresponds to the predicted survival on basis of their EBVps. Results presented in Chapters 3 and 4 of this thesis show that relatively small experimental groups that differ in EBVps also show differences in realized survival in the expected direction.

Physiological characteristics such as glycogen reserves and cortisol levels during late gestation show considerable variation between litters, but also between individual fetuses within litters (Randall and L'Ecuyer, 1976; Kattesh et al., 1997). Therefore, in order to detect physiological differences between litters that differ in EBVps, large numbers of litters or a large contrast in EBVps between those litters is required. In Chapter 5, the difference between the litters with the lowest EBVps and highest EBVps was 16%, indicating an expected difference in realized survival of 16% if those litters were born and reared under the same environmental conditions. Results from Chapter 5 show that it is possible with such a range of EBVps to detect physiological differences that are due to differences in EBVps between litters. This underlines the high reliability of the EBVps and proves that from a population of animals with known EBVps interesting experimental groups can be formed to study the biological background of genetic differences in piglet survival.

Availability of groups of experimental animals with known EBVps offers more opportunities for interesting research, as illustrated by the following example. There is a lot of information available on specific aspects of prenatal development, such as the development of organs like the liver, stomach, and small intestine (reviewed by Van der Lende, 2001). However, little is known about the importance of variation in prenatal development between piglets in relation to variation in piglet survival. For example,

adequate development of the stomach and small intestine is essential for the ability to adapt to the shift from parenteral nutrition before birth to enteral nutrition after birth (reviewed by Sangild et al., 2000). However, little is known about the consequences of between-piglet variation in development of the stomach and the small intestine for postnatal survival and growth of the piglets. Knol (2001) has shown that EBVps are good predictors for postnatal survival of piglets. Measurement of development of any organ (e.g. the stomach or small intestine) in piglets with known EBVps makes it thus possible to determine to which extent between-piglet variation in a specific aspect of organ development is important for variation in piglet survival. In this way, animals with known EBVps may be used to gain more insight in the consequences of between-piglet variation in prenatal development for piglet survival.

6.2. Biological Mechanisms Underlying Genetic Differences in Piglet Survival

Breeding values for piglet survival are estimated on the basis of survival from end of gestation until weaning. Results presented in Chapter 3 and 4 show that differences in survival as a consequence of differences in EBVps are already apparent in the perinatal period (i.e. in the period around birth). This indicates that biological explanations for these survival differences involve processes or factors that play a role in the occurrence of perinatal mortality. The following two paragraphs combine results from Chapters 2 to 5 to summarize our current understanding on the biological background of genetic differences in farrowing survival and postnatal survival.

Farrowing Survival

In Chapter 2, no convincing evidence was found for genetic variation in stillbirth between lines. It was suggested that this does not exclude the existence of genetic variation within lines. Indeed, results in Chapters 3 and 4 show a decrease in stillbirth with increasing EBVps. Intrapartum stillbirth proved to be the largest stillbirth category and showed a significant decrease with increasing EBVps (Chapter 3). Based on results in Chapters 3 to 5, a number of possible biological explanations for the observed decrease in intrapartum stillbirth with increasing EBVps can be postulated.

As intrapartum stillborn piglets are lighter than liveborn piglets, birth weight is considered to be a risk factor for intrapartum stillbirth (Chapter 2 & 3; De Roth and Downie, 1976; Björklund et al., 1987). However, birth weights of intrapartum stillborn piglets were not different between litters with high and low EBVps (Chapter 3), suggesting that birth weight did not explain EBVps-related differences in intrapartum stillbirth.

Prolonged farrowings and longer birth intervals (defined as the time elapsed since the birth of the previous piglet) are associated with an increased risk for intrapartum stillbirth, due to asphyxiation of the piglet (Randall, 1972a; Pejsak et al., 1983). Although the course of farrowing may largely be determined by the sow, the fetus itself may also contribute to a prolonged farrowing through a reduced viability or a deficiency in some possible factor accelerating birth (Svendsen and Bengtsson, 1984). However, results in Chapter 4 demonstrate that differences in the course of farrowing (i.e. duration of farrowing and birth intervals) could not account for the EBVps-related differences in farrowing survival.

It is very important that the umbilical cord remains intact during the birth process, because of its role in gas transport to and from the fetus (Randall, 1989). Premature rupture of the umbilical cord during delivery leads to intrapartum asphyxia, which explains why intrapartum stillborn piglets are frequently born with a broken cord (Randall, 1972b; Zaleski and Hacker, 1993). Therefore, a long and strong umbilical cord might be advantageous with regard to survival during farrowing. Randall (1989) found marked variation between piglets at term in length, strength, and elasticity of the umbilical cord, but did not find any causes of this variation. In Chapter 5, we also observed a large variation between fetuses in umbilical cord length, ranging from 14 to 40 cm. However, we found no relationship between umbilical cord length and EBVps, indicating that there was no underlying genetic variation in umbilical cord length. It cannot be excluded that umbilical cord strength or elasticity are more important characteristics determining the risk for premature umbilical cord rupture. Possible relationships of these characteristics with EBVps may be investigated in future experiments.

Heart glycogen is assumed to be essential for survival during anoxia in fetal lambs, newborn rats, rabbits, and guinea-pigs (Dawes et al., 1959; Shelley, 1961). Heart glycogen provides energy for muscular contractions in absence of oxygen. No data exist on relationships between survival time under anoxia and heart glycogen concentrations in the pig. A study of Randall (1979) demonstrated that heart glycogen concentrations of experimentally asphyxiated pig fetuses were significantly lower than those of control

littermates, suggesting therefore also a role for heart glycogen in the resistance against anoxia in the pig. Our findings that intrapartum stillbirth decreases with increasing EBVps and that heart glycogen levels decrease with increasing EBVps (Chapter 5) therefore are quite contradictory. Considering that only about 0.5% of total body glycogen is present in the heart near term (Okai et al., 1978), it is possible that the contribution of heart glycogen to energy supply during anoxia is minimal compared to other sources. For example, liver glycogen stores are also mobilized during anoxia (Randall, 1979). It is unknown whether liver glycogen is more important during anoxia than heart glycogen, but the observed differences in liver glycogen in relation to EBVps (Chapter 5) may be more important for farrowing survival than the observed differences in heart glycogen.

The supply of oxygen to the fetus during farrowing may be influenced by uterus contractions causing a reduction in placental blood flow (Taverne et al., 1995). One may therefore speculate that a highly vascularized placenta is better able to maintain integrity of placental blood flow than a placenta with less vascularization. Currently, we have no information on relationships between placental vascularization and EBVps. As already discussed in Chapter 5, the observed increased placental efficiency (ratio fetal weight/placental weight) with increasing EBVps may be achieved through a better vascularization. If this is the case, then it is possible that the decreased risk for intrapartum stillbirth in litters with high EBVps can partly be explained by a better oxygen supply to the fetus during farrowing.

Adequate prenatal development of the piglet is essential for its ability to withstand stresses that are associated with the birth process. Glastonbury (1977) found histological differences in the liver, kidneys, and spleen of intrapartum stillborn piglets that suggest immaturity in the development of these organs. Björklund et al. (1987) compared histomorphological organ characteristics of intrapartum stillborn piglets with unaffected liveborn piglets and concluded that the histological picture of liver, kidneys, and thyroid indicated disturbances in the fetal growth pattern of intrapartum stillborn piglets. These authors supported the suggestion of Svendsen (1982) that "the stress of hypoxia during farrowing may be superimposed upon a prior disease or abnormality of affected individuals". Results presented in Chapter 5 provide evidence for a higher degree of development or maturation in litters with a high EBVps. This may indicate that piglets with high EBVps are generally better prepared to withstand the stresses associated with the farrowing process.

Postnatal Survival

Several studies have shown that a longer time interval from birth until first colostrum uptake (FCU) is negatively correlated with subsequent survival chances of the piglet (reviewed by Bünger et al., 1984; Hoy et al., 1995). In Chapter 4 we investigated whether EBVps of the piglet was related to the moment of first colostrum uptake. Both before and after accounting for differences in birth weight, no relationships were found between the moment of first colostrum uptake and EBVps of the piglets. Apparently, the time until first colostrum uptake is not related to the genetic merit of the piglet for survival. This does not exclude an influence of genes of the sow on the moment of first colostrum uptake. In this respect, some preliminary results of our studies on the biological and genetic aspects of mothering ability are worth mentioning. In these studies, the behavioral measurements on the piglets as described in Chapter 4 were related to the genetic merit of the sows for mothering ability. Piglets from sows with a high genetic merit for mothering ability had a significantly shorter interval from birth to first colostrum uptake than piglets from sows with a low genetic merit for mothering ability. Biological explanations for these preliminary results are currently known, but answers are likely to be found in studies that focus on behavioral interactions between sow and piglets early after birth. Maternal behavior characteristics are likely to play a role in behavioral interactions between sow and piglets early after birth (reviewed by Fraser, 1984). For instance, a sow that is very quiet during farrowing provides a more favourable suckling environment for her piglets than a restless sow with frequent posture changes. Furthermore, morphological characteristics of the udder, such as nipple size, but also the way the udder is exposed to the piglets may also influence the time until first colostrum uptake (reviewed by English and Wilkinson, 1982). Finally, a nice example of behavioral interactions between the sow and her piglets early after birth is provided by a study from Morrow-Tesch and McGlone (1990). They have shown that within the first 12 hours after birth, piglets are attracted to specific maternal odors, such as the odor of maternal feces or the odor of lipids produced by the glands surrounding the nipple.

Evidence provided in Chapter 5 suggests that increased postnatal survival rates of liveborn piglets with high EBVps may be related to a higher degree of development or maturity at birth. The observed increased glycogen concentrations in liver and muscle and higher carcass fat percentage in litters with high EBVps may have consequences for postnatal carbohydrate metabolism and thermoregulatory abilities. The observed differences

in relative weights of the small intestine and to a lesser extent the stomach suggest differences in gastrointestinal development that may affect the ability of the piglets to adapt to the shift from parenteral nutrition before birth to enteral nutrition after birth.

As discussed in Chapter 5, the positive relationship between fetal cortisol concentrations and EBVps possibly caused the majority of the observed differences in fetal development and maturity. Increased cortisol concentrations with increasing EBVps may reflect alterations in functioning and/or regulation of the HPA axis during late gestation (Randall, 1983; Silver and Fowden, 1989). The following section will discuss more in detail the development of the HPA axis during late gestation.

6.3. Hypothalamus-Pituitary-Adrenal Axis During Late Gestation

The development and maturation of the HPA axis during late gestation shows considerable variation between various species (reviewed by Dalle et al., 1985; reviewed by Liggins, 1994). Species like rat, mouse, human, and guinea pig show no profound changes in fetal adrenal activity when birth approaches. Newborns of these species can be characterized as relatively immature and highly dependent on maternal care. On the other hand, species that are relatively mature at birth, such as sheep, cow, or pig, exhibit a marked increase in adrenal activity during late gestation. Depending on the species, increased activity of the HPA axis during late gestation has an important role in development and maturation of various organ systems and plays a role in initiation of the birth process. Characteristics of development of the HPA axis during late gestation will be discussed for various species in the following sections. Of course, main emphasis will be on the development of the HPA axis of the pig.

Adrenal Growth and Cortisol Levels During Late Gestation

In rats, mice, humans, and guinea-pigs, adrenal growth during late gestation is slower than growth of the whole body (reviewed by Dalle et al., 1985). This could be due to a decrease in stimulatory activity of the pituitary, as demonstrated in rats and guinea-pigs (Jones and Roebruck, 1980; Dupouy and Chatelain, 1981). In these species, fetal cortisol

levels rise slowly during late gestation and maternal levels are considerably higher than fetal levels. It has been shown that in these species, maternal cortisol can contribute to fetal cortisol levels (reviewed by Dalle et al., 1985). For instance, in guinea-pigs at the end of gestation, 90% of fetal cortisol was of maternal origin and the secretion rate and metabolism of the fetal adrenal was very low (Dalle and Delost, 1976).

Fetal lambs, calves, and pigs exhibit increased adrenal growth during late gestation (reviewed by Dalle et al., 1985). In the pig, Lohse and First (1981) reported a faster increase in adrenal weight relative to body weight from about 77% of gestation. During this stage of gestation, the ultrastructure of the adrenal cortex of the fetal pig already resembles that of the adult and therefore is said to mature very early during gestation. In contrast, in the fetal sheep the adrenal cortical cells are immature until 90% of gestation (Robinson et al., 1979).

In the pig, the weight and volume of the adrenal gland show a more pronounced change between days 105 to 113 of gestation (Lohse and First, 1981; Nicolle and Bosc, 1989). Fetal cortisol levels start to rise concomitantly with the increased adrenal growth from approximately day 105 of gestation (Randall, 1983; Silver and Fowden, 1989). There is extensive evidence that these increased fetal cortisol levels are primarily due to an increased cortisol secretion by the fetal adrenal (Lohse and First, 1981; Nicolle and Bosc, 1989; Klemcke, 1995). From day 105 of gestation, the adrenal cortex, which contains cells with steroidogenic activity, shows increased growth relative to the adrenal medulla (Nicolle and Bosc, 1989). This growth of the cortex was primarily due to hyperplasia, but some hypertrophy also occurs (Lohse and First, 1981). The increase in fetal cortisol levels during late gestation is not accompanied by a concomitant increase in maternal cortisol levels. Maternal levels rise slowly during late gestation and exhibit a sharp increase during birth rather than before birth (Randall, 1983). In the pig, Klemcke (1995) showed that the maternal contribution to fetal cortisol decreased from around 20% at day 50 of gestation to only 6% at day 100 of gestation.

Control of the Prepartum Rise in Cortisol Levels

ACTH

Adrenocorticotropic hormone (ACTH) is synthesized by the fetal pituitary and is responsible for fetal adrenal development. The moment at which the fetal adrenal is capable of responding to ACTH varies between species. In the sheep, the ACTH response is highest

before 40% and after 90% of gestation, with little response in the intervening period (Wintour et al., 1975; Glickman and Challis, 1980). In the foal, there was no detectable increase in plasma cortisol in response to exogenous ACTH until a few days before birth (Silver and Fowden, 1988 in Silver and Fowden, 1989). In the pig, there is evidence that the fetal adrenal is capable of responding to exogenous ACTH from as early as day 70 of gestation (Silver and Fowden, 1989). Responsiveness of the fetal adrenal to ACTH correlates well with the changes seen in ultrastructure of the adrenal cortex. Growth of the cortical zone depends on the pituitary, whereas growth of the medulla was not affected by hypophysectomy (Nicolle and Bosc, 1989).

The precise mechanism by which the late gestational rise in fetal cortisol is achieved and the role of ACTH herein is still unclear. Silver and Fowden (1989) have shown in chronically catheterized fetal pigs that fetal plasma cortisol levels rise concomitantly with fetal plasma ACTH levels during the last six days of gestation. Fetal plasma cortisol levels are significantly correlated with fetal ACTH levels from day 70 of gestation until term. However, the slope of the regression line that was fitted for the relationship between fetal cortisol and ACTH was significantly higher from day 100 until term than from day 70 to day 100. Therefore, these authors suggested that increased sensitivity of the adrenals to ACTH may explain the increase in fetal cortisol levels seen in the last few days of gestation. In contrast, Lohse and First (1981) measured in vitro adrenal cortisol production in response to ACTH stimulation between day 89 and day 113 of gestation and observed no changes in the ACTH dose-response during this period. Klemcke (1992) reported an increase in adrenal cortisol content between days 90 and 105 of gestation, but this increase was accompanied by reduced concentrations of adrenal ACTH receptors. He therefore suggested that the possible increased adrenal responsiveness to ACTH is not mediated via ACTH receptors. In the fetal sheep, cortisol itself may enhance responsiveness of the fetal adrenal to ACTH and thus may contribute in this way to the prepartum rise in cortisol (reviewed by Liggins, 1994).

Corticosteroid Binding

Both unbound and low-affinity protein-bound (albumin-bound) cortisol are considered to be biologically active, while cortisol that is bound to high-affinity proteins (corticosteroid-binding globulin, CBG) is inactive. In species like mice, rats, baboon, human, and guinea-pigs, maternal and fetal CBG levels are closely correlated and the slow increase in free cortisol levels in late gestation is apparently due to a decrease in fetal CBG concentrations

(reviewed by Dalle et al., 1985). In the pig and sheep, fetal CBG levels increase preceding to the observed rise in fetal cortisol levels (Fairclough and Liggins, 1975; Kattesh et al., 1997). In these species, CBG may have a role in protecting the fetus against high levels of free cortisol that may induce premature maturation or premature initiation of parturition (Kattesh et al., 1997).

Placental Enzymes

The placental enzyme 11ß-hydroxysteroid dehydrogenase (11ß-HSD) catalyzes the interconversion of biologically active cortisol to various inactive forms (e.g. cortisone). The role of placental 11ß-HSD in regulation of fetal cortisol levels varies widely with species and stage of gestation (reviewed by Dalle et al., 1985). Placental 11ß-HSD has been characterized in the rat, sheep, baboon, and human, where it may act as a barrier to protect the fetus against high maternal cortisol concentrations (reviewed by Burton and Waddell, 1999). In addition, in these species, placental 11ß-HSD may play an important role in the regulation of fetal maturation by controlling the amount of cortisol to which the fetuses are exposed during gestation (Klemcke and Christenson, 1996).

The first evidence for the existence of porcine placental 11ß-HSD was provided by Klemcke and Christenson (1996). These authors observed an increase in placental 11ß-HSD activity between day 50 and day 100 of gestation. This increase in activity may indicate an increase in effectiveness of the placental barrier to protect the fetus against maternal cortisol. An increase in placental 11ß-HSD activity may also indicate a role for this enzyme in keeping fetal levels of biologically active cortisol low until the prepartum rise in cortisol is needed near term. Evidence for the ability of placental 11ß-HSD to convert fetal cortisol to cortisone is provided by Klemcke (1995), who found that 50% of fetal cortisone originated from maternal cortisol, implying that the other 50% must originate from fetal cortisol.

Function of the Rise in Cortisol

Cortisol regulates development and maturation during fetal life, rather than supporting survival in adult life (Muglia et al., 1995). In general, cortisol prepares the fetus for the transition from intrauterine to extrauterine life. Cortisol stimulates and regulates maturation

and development of a wide range of organs that have important functions in assuring survival after birth (reviewed by Liggins, 1994).

In Chapter 5, the functions of cortisol in glycogen deposition and maturation of the gastrointestinal tract were already discussed. In the following paragraphs, these functions will be reviewed in more detail for the pig, but also for other species. Furthermore, the roles of cortisol in development of fetal gluconeogenic capacity and development of the thyroid are reviewed on basis of the literature. Relationships of fetal gluconeogenic capacity and thyroid development with EBVps were not investigated in this thesis, but are likely to exist, due to the strong positive relationship between cortisol and EBVps.

Finally, evidence for the role of cortisol in the initiation of parturition in the pig will briefly be reviewed.

Glycogen Deposition

Heart glycogen levels decrease near term in most species (e.g. rhesus monkey, sheep, guinea-pig) but seem to remain rather constant in the pig (Shelley, 1961; Randall and L'Ecuyer, 1976). In the fetal lamb and rabbit, no evidence is found for a regulatory role of cortisol in the metabolism of heart glycogen during late gestation (Barnes et al., 1978; Bhavnani et al., 1986). As shown in Chapter 5 and also in other studies (Fowden et al., 1985; Randall, 1987; Randall, 1988), cortisol is also not involved in the control of heart glycogen levels in the pig. To our knowledge, factors involved in deposition or breakdown of heart glycogen during gestation are currently unknown.

Liver glycogen concentrations start to rise from about day 70 of gestation, with a higher rate of deposition from about day 100 of gestation (Randall and L'Ecuyer, 1976; Okai et al., 1978; Fowden et al., 1995). The increase in the latter period of gestation coincides with the changes seen in prepartum cortisol levels. Indeed, in the rat, rabbit, and sheep there is convincing evidence for the stimulating role of cortisol in liver glycogen deposition (Jost and Picon, 1970; Barnes et al., 1978). As shown in Chapter 5 of this thesis and various other literature reports, cortisol also stimulates liver glycogen deposition in the pig (Fowden et al., 1985; Randall, 1988; Fowden et al., 1995).

Skeletal muscle glycogen levels rise in most species before term (reviewed by Shelley, 1961). In the fetal lamb, cortisol does not seem to be involved in muscle glycogen deposition, as demonstrated by studies of Barnes et al. (1977) and Barnes et al. (1978). In contrast, evidence for a stimulating role of cortisol in late prenatal skeletal muscle glycogen

deposition in the pig is provided by various studies (Fowden et al., 1985; Randall, 1987; Randall, 1988) and also by results in Chapter 5 of this thesis. In general, effects of cortisol on muscle glycogen deposition are not as pronounced as effects seen on liver glycogen deposition, suggesting that other factors also may be involved.

Lung glycogen is concentrated in the cells of the alveolar epithelium. In many species, including the pig, concentrations of lung glycogen reach a peak somewhere during gestation and subsequently fall to very low levels just before birth (reviewed by Shelley, 1961; Randall and L'Ecuyer, 1976; Okai et al., 1978). The decrease in lung glycogen is concomitant with the increase in lung surfactant produced by alveolar epithelial cells, suggesting that glycogen is used as substrate for surfactant synthesis (Maniscalco et al., 1978). Lung surfactant facilitates expansion of the lungs after birth. In pigs and mice, cortisol stimulates glycogenolysis (i.e. breakdown of glycogen to glucose) in the lung during gestation and therefore enhances lung maturation through increased production of lung surfactant (Bourbon and Jost, 1982; Fowden et al., 1985). Besides enhancing glycogenolysis, other effects of cortisol on prenatal lung development include stimulation of connective tissue maturation, alveolar epithelial differentiation, lung liquid resorption, and antioxidant enzyme activity (reviewed by Liggins, 1994).
As shown in Chapter 5, lung weights did not differ at day 111 of gestation between litters with different EBVps. However, a more detailed study of lung development in relation to EBVps will provide more insight in the consequences of the observed increased cortisol levels with increasing EBVps on prenatal lung maturation.

Gluconeogenesis

Gluconeogenesis is the process in which glucose is produced from various precursors, such as lactate, pyruvate, glycerol, and amino acids. The conversion of these precursors to glucose is catalyzed by various gluconeogenic enzymes, such as glucose-6-phosphatase, fructose diphosphatase, pyruvate carboxylase, and PEP carboxykinase. In various species, highest activities of gluconeogenic enzymes are seen immediately after birth, when adequate glucose supply is needed to the tissues, especially in the period before colostrum uptake (Fowden and Silver, 1991). The role of cortisol in the stimulation of gluconeogenic enzyme activity has been demonstrated in the sheep (Fowden et al., 1993), but may also be true for the horse and the rat (Silver, 1990; reviewed by Liggins, 1994). Fowden et al. (1995) studied the role of the prepartum rise in cortisol on gluconeogenic enzyme activities in the fetal pig.

Cortisol infusion in fetuses during late gestation significantly increased glucose-6-phosphatase activity in the liver, kidneys, and duodenum. No effects of cortisol were found on other gluconeogenic enzyme activities. Significant positive correlations were found between glucose-6-phosphatase and cortisol, but not between other gluconeogenic enzymes and cortisol. Glucose-6-phosphatase is not only the rate-limiting enzyme of gluconeogenesis but also of glycogenolysis. Thus, the experiments of Fowden et al. (1995) indicate that the prepartum rise in cortisol may play a major role in the capacity of the newborn pig to produce glucose both from glycogen and from various precursors.

These observations suggest that glucose-6-phosphatase activity also may have been enhanced in litters with high EBVps, due to higher circulating cortisol concentrations. If so, this would imply that piglets with high EBVps have an increased capacity to produce glucose from their increased liver glycogen stores, as well as from various other precursors.

Gastrointestinal Tract

In the last four weeks preceding parturition, the weight increment of the porcine stomach relative to the whole body remains constant, whereas there are considerable changes in gastric function (reviewed by Sangild et al., 2000). Gastric acid secretion starts at least 11 days before term (Foltmann et al., 1987) and is important for postnatal activation of gastric proteases (reviewed by Cranwell, 1995). Prochymosin and pepsinogen A are examples of gastric proteases and are synthetized as proenzymes by the chief cells of the fundic glands of the stomach during the last four weeks of gestation (reviewed by Sangild et al., 2000). In their active forms, these enzymes have milk-clotting and proteolytic activities. The prepartum rise in cortisol parallels the major changes in gastric acidity and stimulates synthesis of prochymosin and pepsinogen A (Sangild, 1995). Thus, these prenatal effects of cortisol on gastric function may be important to secure adequate gastric digestive capacity in the newborn pig.

In fetal lambs and pigs, the growth rate of the small intestine is higher than that of the whole body during the last three weeks of gestation (reviewed by Sangild et al., 2000). Carbohydrases (e.g. lactase) and aminopeptidases (e.g. aminopeptidase N; aminopeptidase A) are small intestinal enzymes that are required for digestion of carbohydrates and proteins, respectively, after birth. In the pig, the activity of these enzymes starts to increase from about day 100 of gestation in certain regions of the small intestine (Sangild et al., 1995). The prepartum rise in fetal cortisol stimulates activities of these enzymes, as evidenced by higher

enzyme activities in cortisol-infused fetuses compared to non-infused fetuses at day 82-96 of gestation (Sangild et al., 1995). In addition, plasma cortisol levels and activities of these enzymes were positively correlated in non-infused fetuses. These stimulative effects of cortisol have also been reported in rats, humans, and sheep (reviewed by Sangild et al., 2000).

The capacity of the small intestine to absorb glucose and macromolecules (including immunoglobulins) increases during the final weeks of gestation. Evidence in literature points towards a stimulating role of cortisol in the uptake of immunoglobulins by the small intestine after birth (reviewed by Sangild et al., 2000).

Taken together, cortisol seems to play an important role in the preparation of the gastrointestinal tract for the change in diet that occurs at birth. Therefore, increasing fetal cortisol levels with increasing EBVps (Chapter 5) may imply that litters with high EBVps have an increased ability to adapt to the change in nutrition at birth. This may not only have consequences for uptake and digestion of nutrients, but also for uptake of maternal antibodies.

Thyroid

In the pig, the responsiveness of the thyroid appears to be fully developed at birth. This is evidenced by an abrupt rise in plasma levels of thyroid hormones (T_3 and T_4) during the first six hours of life (Berthon et al., 1993). Thyroid hormones play an important role in the regulation and maintenance of thermogenesis directly after birth (Ślebodziński, 1988; Dauncey, 1990; Berthon et al., 1993).

In order to develop the potential for high demand of T_3 and T_4 directly after birth, the thyroid maintains a relatively high rate of T_4 production during gestation. However, there is no need for the fetus to increase its metabolic rate *in utero* and thus circulating levels of biologically active T_3 have to remain relatively low. This is achieved through deiodination of T_4 to inactive reverse T_3 (rT_3) instead of T_3 and by a high placental metabolic clearance rate of T_3. During late gestation, cortisol influences the switch from fetal to newborn state by stimulating deiodination of T_4 to T_3 and by reduction of the placental metabolic clearance rate of T_3. The resulting rise in T_3 levels occurs parallel to the increase in fetal cortisol levels (reviewed by Liggins, 1994).

In the experiment described in Chapter 5, we did not measure T_3 levels during late gestation in litters that differ in EBVps. However, the positive relationship between fetal

cortisol levels and EBVps may have consequences for early neonatal regulation and maintenance of heat production through an influence on thyroid development.

Initiation of Parturition

In ruminants (e.g. sheep, cow, and goat) increased activity of the fetal HPA axis causes hormonal changes that eventually lead to the initiation of parturition (Liggins et al., 1973; Thorburn and Challis, 1979). In sheep, the increase in plasma cortisol activates expression of placental enzymes that convert progesteron to oestrogen. An increase in the oestrogen/progesteron ratio leads to enhanced production of prostaglandins which subsequently stimulate myometrial contractility.

In the pig, there is conflicting evidence on the involvement of the fetal HPA axis in the onset of parturition. Early studies of Bosc (1973) and North et al. (1973) showed that ACTH infusion of fetuses around day 103 of gestation resulted in parturition 7 to 8 days later. Stryker and Dziuk (1975) reported that fetal decapitation of all fetuses within a litter at day 40 to 50 of gestation prolonged gestation beyond 120 days. Presence of more than one intact fetus in a litter containing some decapitated fetuses did not delay parturition. Therefore, it was suggested that the onset of parturition may be determined by a minority of the fetuses. In more recent studies of Silver and Fowden (1989) and Randall et al. (1990), infusion of fetuses with ACTH on or after day 100 of gestation resulted in a rise of fetal plasma cortisol levels, but did not induce premature parturition. Silver and Fowden (1989) concluded that the fetus has a role in the onset of parturition, but that the actions of fetal cortisol in the sequence of hormonal events leading to delivery probably differ from ruminants.

If the prepartum rise in fetal cortisol plays some role in the onset of parturition in the pig, then the question arises if parturition will be initiated at an earlier stage in litters with high EBVps, since these litters exhibit higher cortisol levels on day 111 of gestation (Chapter 5). However, this does not seem likely, because Knol (2001) showed that the genetic correlation between piglet survival and gestation length is positive, indicating that selection for increased survival will prolong rather than shorten gestation length.

Variation in HPA Axis

Considerable differences in timing and magnitude of the prepartum rise in cortisol levels have been observed between individual fetuses within a litter and between litters (Randall,

1983; Kattesh et al., 1997). Furthermore, Randall et al. (1990) observed considerable variation between individual fetuses in the response to ACTH infusion from day 103 of gestation. Randall (1983) suggested that, apart from variation caused by the surgery or sampling procedures, variation in cortisol levels may have been due to individual differences between fetuses in the timing and/or degree of adrenal maturation.

In the experiment described in Chapter 5, 39% of the differences seen in fetal cortisol levels at 111 days of gestation could be attributed to differences in EBVps between litters. Therefore, the observed differences in developmental patterns of cortisol release and ACTH response in the studies of Randall (1983), Randall (1990), and Kattesh et al. (1997) partly may have been due to genetic differences between fetuses in development or maturation of the fetal HPA axis.

6.4. Physiological Characteristics of Meishan Piglets and Piglets From Genetically Obese Lines

The Meishan pig belongs to the Taihu group of breeds and originates from the area around Lake Taihu to the west of Shanghai in the People's Republic of China. The Meishan pig is of great interest in research on reproductive performance, due to its high prolificacy. The three to five piglets higher litter size of Meishan pigs compared to European and U.S. breeds can be explained by a higher percentage of embryonic survival between days 12 and 18 of gestation and probably by a higher uterus capacity (Bazer et al., 1988; Wilson et al., 1999).

As already noticed by Knol (2001), various characteristics of the Meishan pig and other genetically obese lines show striking similarities with litters that have a high genetic merit for piglet survival. The following paragraphs will discuss similarities between results presented in this thesis and characteristics of both Meishan pigs and piglets from genetically obese lines.

Uterus and Placental Development

Litters with high EBVps show similarities with Meishan piglets in various uterus and placental characteristics. At day 90 of gestation, the empty uterine weight of Meishan gilts is

significantly lower than that of Yorkshire gilts (Wilson et al., 1998). Results on uterine weight were not shown in Chapter 5, but indicate a significant decrease in empty uterine weight with increasing EBVps. Knight et al. (1977) suggested that decreased uterine weight may be associated with lower oestrogen levels, which are known to cause fluid accumulation in uterine tissue. Results presented in this thesis do not provide evidence for a role of oestrogens in the decreased uterine weight in litters with high EBVps, as estradiol-17ß levels were not related to EBVps of the litter (Chapter 5). At term, Meishan piglets have lighter and more efficient placentae than Yorkshire piglets (Wilson et al., 1998). By comparison, average placental weight significantly decreased with increasing EBVps and average placental efficiency tended to increase with increasing EBVps (Chapter 5).

Birth Weight and Piglet Survival

The higher litter size of Meishan vs. European or U.S. breeds is associated with lower birth weights of Meishan piglets (Lee and Haley, 1995). Similarly, piglets from obese lines have lower birth weights than piglets from lean lines (Mersmann et al., 1982; Mersmann et al., 1984). At a given birth weight, Meishan and obese piglets have higher survival rates than Large White or lean piglets (Mersmann et al., 1984; Lee and Haley, 1995), respectively. Selection for increased piglet survival is not associated with a significant reduction in birth weight (Knol 2001), although piglets may become somewhat shorter in length (Chapter 5). Litters with high EBVps have higher survival rates at a given birth weight than litters with low EBVps (Chapter 4; Knol, 2001). These differences become especially obvious at lower birth weights (< 1.5 kg).

Physiological Maturity at Birth

As discussed in section 6.2, increased farrowing and postnatal survival with increasing EBVps may be realized through a higher degree of development or maturity at birth. Similar suggestions have been made in studies investigating the physiological basis for the higher survival rates of Meishan and obese piglets compared with Large White and lean piglets, respectively (Stone, 1984; Mersmann et al., 1984; Herpin et al., 1993). Based on differences in body and tissue composition, metabolic and hormonal state, and fat metabolism at birth, Herpin et al. (1993) suggested that selection for lean tissue growth may result in less mature

piglets at birth. Similar conclusions were drawn in studies of Stone (1984) and Mersmann et al. (1984). In this respect, it is interesting to note that several studies report elevated fetal cortisol levels in late gestation or at birth in Meishan and genetically obese piglets compared with Large White and genetically lean piglets, respectively. Hoffman et al. (1983) found no differences in plasma cortisol between lean and obese piglets until day 100 of gestation, but observed a spectacular five-fold increase at day 110 in obese piglets compared to only a two-fold increase in lean piglets. Martin et al. (1985) reported higher cortisol levels at day 110 of gestation in fetuses of high backfat sows compared to fetuses of low backfat sows. Herpin et al. (1993) found significantly higher cortisol levels at birth in Meishan piglets compared to Large White piglets and piglets from a genetically lean line.

Thermoregulatory Abilities

Meishan piglets and genetically obese piglets have higher body fat percentages at birth than Large White or genetically lean piglets (Hoffman et al., 1983; Herpin et al., 1993). Results in Chapter 5 show that the percentage of carcass fat at day 111 of gestation increases with increasing EBVps.

Herpin et al. (1993) suggested that the differences in percentage body fat between Meishan and genetically lean piglets may be important with regard to postnatal energy metabolism and survival. In this respect, recent observations of Herpin and Hulin (2000) are of particular interest. These authors showed that Meishan piglets weighing less than 1125 g at birth have similar abilities to increase heat production and reduce heat loss during a cold challenge than Meishan piglets that weigh more than 1125 g. In contrast, crossbred Large White × Piétrain piglets clearly showed impairment of heat production and a reduced ability to decrease heat loss in the cold below a birth weight of 1125 g. The authors suggested that in Meishan piglets, insulation is apparently not affected by birth weight and that the better cold resistance of Meishan piglets could partly be explained by their higher ability to metabolize fat. This latter observation is in agreement with results of Herpin et al. (1993), where Meishan piglets exhibited a greater ability to metabolize fat during the early neonatal period in comparison to genetically lean piglets. Considering the positive relationships of carcass fat percentage and muscle glycogen concentrations with EBVps (Chapter 5), it will be interesting to investigate thermoregulatory abilities of newborn piglets with different EBVps in future experiments.

6.5. Practical Implications

Improved Understanding of the Consequences of Selection

The results of this thesis increase our understanding of the extent to which animals with different genetic merit for piglet survival differ from each other in a biological way. As already mentioned in the definition of the objectives of this thesis (Chapter 1), this may lead to more insight in the consequences of selection. Some examples on how the results of this thesis contribute to a better understanding of the consequences of selection are given below.

Results presented in this thesis (Chapter 4) and in the thesis of Knol (2001) show that differences in survival rate between litters with different EBVps depend on birth weight. The differences in survival between litters with high and low EBVps are most pronounced at birth weights below approximately 1.5 kg. Above this birth weight, differences in survival are much smaller. Considering that EBVps might be related to physiological maturity, these birth weight-dependent differences in survival are easier to understand. After all, lighter piglets at birth are more likely to benefit from an increased amount of glycogen or fat reserves than heavier piglets.

As already pointed out in Chapter 1, piglet mortality can be reduced to very low levels if nutritional, managemental, and husbandry conditions are optimal. For example, even very weak piglets at birth can be saved if they are kept in a warm environment and are provided with sufficient colostrum directly after birth. Therefore, we may speculate that the importance of an adequate development or maturity at birth for survival is likely to be lower when environmental conditions are kept optimal. This suggests that the largest differences in survival between litters which differ in EBVps can be expected under somewhat more adverse conditions.

From the above we may conclude that the responses to selection for increased piglet survival under field conditions are likely to depend on birth weight and environmental conditions. This agrees well with results from studies that attempted to increase piglet energy reserves by manipulation of the sow's diet during late gestation. Pettigrew (1981) and Pluske et al. (1995) reviewed the effects of fat supplementation on piglet performance and concluded that adding fat to the sow's diet during late gestation increases milk production, increases the percentage of fat in colostrum and milk, may increase glycogen

reserves, and slightly increases piglet carcass fat stores at birth. The greatest effects of supplemental dietary fat on piglet survival were seen at low birth weights and in herds where the survival rate was low (less than 80%).

Knol (2001) has shown positive genetic correlations of the direct genetic (piglet) effect of preweaning surival with feed intake and weight gain when measured in the body weight range between 29 and 130 kg. In Chapter 5 of this thesis, the positive relationship of relative stomach weight and relative small intestinal weight with EBVps at day 111 of gestation suggests differences in gastrointestinal development between litters that differ in EBVps. Thus, it is possible that the positive genetic correlation of the direct genetic effect of preweaning survival with feed intake and growth is due to a better gastrointestinal development of litters with a high EBVps compared to litters with low EBVps.

Selection for piglet survival will lead to an increase in backfat when measured at 78 and 130 kg body weight (Knol, 2001). This observation correlates well with results from this thesis, which show a significant positive relationship between carcass fat percentage and EBVps at day 111 of gestation. It is possible that differences in backfat at later ages reflect differences in fat deposition already present during fetal development.

Selection on Underlying Biological Traits

Selection for piglet survival on the basis of EBVps requires large scale registration of individual piglet survival. In situations where labor is expensive and thus large scale survival registration not possible, selection on underlying biological traits may be an alternative. If the underlying biological trait shows a higher heritability than the trait survival as such, then genetic progress in piglet survival may even be enhanced at a greater rate compared to selection on basis of EBVps. Useful biological indicators for genetic merit for piglet survival should be easy to measure in the field against relatively low costs. In this thesis we have identified several biological traits that are related to EBVps. The possibilities to select for these traits in order to genetically improve piglet survival will be evaluated in the following paragraphs.

Litters with high EBVps not only have higher preweaning survival rates than litters with low EBVps, but also higher farrowing survival rates (Chapters 3 and 4; Knol, 2001). This suggests that selection for piglet survival on the basis of EBVps will not only lead to improvement of preweaning survival, but will also improve farrowing survival. Knol (2001) reported low to moderate genetic correlations (0.14 to 0.28) between farrowing survival and preweaning survival. This indicates that selection on farrowing survival alone is not expected to increase preweaning survival to a large extent. However, selection on farrowing survival may be considered as an alternative for direct selection on piglet survival in situations where it is not possible to register individual preweaning survival.

In this thesis we have shown that fetal cortisol concentrations during late gestation exhibit a strong positive relationship with EBVps. Considering this strong relationship, the question arises whether selection for fetal cortisol can be used as an alternative for selection on the basis of EBVps. As mentioned above, biological selection parameters should be easy to measure under practical conditions. However, fetal cortisol levels at the end of gestation are impossible to measure under field conditions, because sampling procedures for fetal blood (e.g. fetal catheterization) are technically very difficult. The use of cortisol levels of newborn piglets as a measure for fetal values is not a good alternative, because possible stress experienced during birth process may influence piglet cortisol concentrations (Randall, 1983). Furthermore, cortisol levels of newborn piglets begin to decrease already at 6 hours after birth to reach adult levels by approximately 24 hours after birth (Herbein et al., 1977). The use of maternal cortisol concentrations during late gestation as a measure for fetal levels is not possible, since maternal cortisol levels do not reflect fetal values. For example, maternal cortisol concentrations were also measured in the experiment described in Chapter 5, but no significant correlation was found between maternal and fetal levels ($r = +0.23$; $P = 0.12$). Taken together, cortisol shows a very strong relationship with EBVps, but cannot be used in the field as a selection parameter for piglet survival.

Liver glycogen, muscle glycogen, and body fat are important for cold resistance of newborn piglets, especially in the period before uptake of colostrum. The positive relationships of liver and muscle glycogen concentrations, and carcass fat percentage with EBVps suggest that piglets with high EBVps may be more resistant against the cold than piglets with low EBVps. Thus, the differences in survival rates between piglets with low and high EBVps may (partly) be explained by differences in cold resistance. If so, then selection for cold resistance may be an interesting alternative for genetic improvement of piglet

survival. In sheep, there is convincing evidence for the existence of genetic variation for cold resistance. Slee (1978) reported significant breed differences in the cold resistance of newborn lambs. Slee and Stott (1986) showed that cold resistance of neonatal lambs can be influenced by genetic selection and estimated the heritability of cold resistance to be 0.17. To our knowledge, no data are yet available whether selection for cold resistance is effective in improving lamb survival in the field. The high heritability (0.17) for cold resistance in neonatal lambs (Slee and Stott, 1986) and the fact that cold resistance is relatively easy to measure in the field, suggest that it might be worthwhile to investigate whether it is possible to apply selection for early neonatal cold resistance in the pig. One negative aspect of selection for cold resistance is that piglet vitality may be reduced as a consequence of the imposed cold stress during the cold resistance test. One way to circumvent this would be indirect assessment of cold resistance by means of non-invasive techniques.

A very promising technique in this respect is the measurement of body glycogen by magnetic resonance spectroscopy techniques, such as the nuclear magnetic resonance (NMR) methodology. NMR spectroscopy is a non-invasive technique that enables in vivo measurements of glycogen concentrations in a wide range of organs, such as liver, muscle, and brain (Gruetter et al., 1994; Price et al., 1999). The use of NMR as a reliable technique to measure *in vivo* glycogen concentrations has already been validated in humans, rats, mice, and rabbits (Gruetter et al., 1994; Cohen et al., 1998; Changani et al., 1998; Price et al., 1999). If also valid in the pig, NMR could be used to measure liver and muscle glycogen concentrations of piglets directly after birth. Selecting piglets for breeding on the basis of their muscle and liver glycogen concentrations may lead to genetic improvement in piglet survival if muscle and liver glycogen concentrations at birth are sufficiently heritable and genetically correlated with piglet survival. The purchase of NMR equipment will involve a substantial investment for the breeding organization, but may be profitable in the long term if selection for glycogen leads to a permanent improvement in piglet survival.

Chapter 5 has shown significant positive relationships of relative weights of the stomach, small intestine, and adrenals with EBVps. Therefore, if organ weights are measured at birth, a simple index of relative organ weights could be made and subsequently used for genetic selection. However, the use of such an index does not seem very realistic, since it implies that piglets have to be sacrificed after birth. Measurement of organ weights of dead piglets is not an option, because organs of piglets that died in the perinatal period differ considerably from organs of unaffected piglets (Björklund et al., 1987).

6.6. General Conclusions

1. The usefulness of EBVps as accurate pedictors for realized survival from end of gestation until weaning has been validated by Knol (2001). This thesis shows that from a population of animals with known EBVps interesting experimental groups can be formed to study the biological background of genetic differences in piglet survival.

2. Underlying biological mechanisms of genetic differences in piglet survival involve processes or factors that play a role before birth, rather than during or after birth.

3. The very strong relationship between fetal cortisol and EBVps suggests genetically determined differences in the development and(or) maturation of the hypothalamus-pituitary-adrenal (HPA) axis during late gestation.

4. Differences in development and(or) maturation of the HPA axis may influence fetal development and maturation through effects on organ development and glycogen deposition.

5. The biological basis for increased piglet survival with increasing EBVps shows similarities with biological mechanisms that are likely to explain the higher survival rates of Meishan vs. Large White piglets and piglets from genetically obese vs. lean lines. Therefore, results of studies that compare physiological characteristics of Meishan with Large White piglets or genetically obese with lean piglets, will contribute to our understanding of the biological background of genetic differences in piglet survival within Western breeds.

6. Research on biological aspects of genetic differences in piglet survival contributes to our understanding of the practical consequences of selection for increased piglet survival.

7. The possibility to measure glycogen reserves of newborn piglets by a non-invasive technique such as nuclear magnetic resonance (NMR) offers interesting opportunities to genetically improve piglet survival in situations where large scale registration of individual preweaning piglet survival is not possible.

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Summary

On average, 3 to 8% of the total number of piglets are delivered stillborn. In addition, another 5 to 30% of live-born piglets dies until weaning (i.e. preweaning mortality). The major cause of stillbirth is asphyxiation of the piglet during parturition. On average, between 50-70% of preweaning mortality occurs within the first three days after birth. The major causes of preweaning mortality are starvation and overlying by the sow.

Piglet survival is likely to remain an important issue in the pig industry of the future. Increasing selection pressure on litter size and lean tissue growth may lead to less mature piglets at birth. This may adversely affect survival rate.

Apart from optimizing environmental conditions, it is also possible to increase piglet survival by genetic selection. In populations with reliable registration of farrowing survival and pre-weaning survival, genetic variation can be quantified by the estimation of breeding values for piglet survival (EBVps). Estimated breeding value for piglet survival of an individual piglet represents its genetic merit to survive from onset of farrowing until weaning. The biological background of genetic differences in piglet survival can be investigated by measurement of survival-related biological parameters in animals that differ considerably in EBVps.

The main objective of this thesis was to gain insight in the biological backgrounds of genetic differences in piglet survival. Although the genetics of piglet survival involve both a maternal (sow) and a direct genetic (piglet) component, the experiments described in this thesis focussed only on the direct genetic component.

In Chapter 2, a large data set of approximately 8,000 litters was analyzed to investigate line differences in stillbirth and relationships between stillbirth and various other traits. Number of stillbirths per litter did not differ between lines, neither before nor after adjustment for gestation length (GL), total number of piglets born (TNB), average birth weight of the litter (ABW), and variation in birth weight within the litter (VBW). Number of stillborn piglets per litter increased with decreasing GL, increasing TNB, and decreasing ABW, but was not related to VBW. On average, number of stillborn piglets increased between the second and the fifth parity. Litters with more stillborn piglets also had a higher preweaning mortality of live-born piglets. In conclusion, stillbirth did not differ between lines, but the existence of genetic variation within lines cannot be excluded.

Chapter 3 investigated the moment of death in the perinatal period in relation to genetic merit for piglet survival, using records of 336 litters with known EBVps. Both stillbirth and

early neonatal mortality (within 12 h after birth) decreased with increasing EBVps. Significant decreases with increasing EBVps were observed for number of non-fresh stillbirths, prepartum stillbirths, and intrapartum stillbirths. Intrapartum stillbirth was the most frequent stillbirth category, accounting for almost 67% of all stillborn piglets. As reduced non-fresh, prepartum, and intrapartum stillbirth with increasing EBVps could not be explained by differences in birth weight, other biological processes may play a role.

The progress of farrowing and early postnatal behavior of piglets in relation to genetic merit for piglet survival were studied in Chapter 4. After adjustment for birth weight, both farrowing survival and early postnatal survival significantly increased with increasing EBVps. The progress of farrowing (i.e. duration of farrowing and birth intervals) was not related to EBVps. Piglet vitality was measured by various behavioral indicators, such as the time from birth until first upright standing or the time from birth until first colostrum uptake. None of the behavioral indicators of piglet vitality were related to EBVps, neither before nor after adjustment for birth weight. In conclusion, increased farrowing survival and early postnatal survival with increasing EBVps could not be explained by differences in progress of farrowing or differences in early postnatal piglet behavior.

Relationships between various characteristics of late fetal development and genetic merit for piglet survival were investigated in Chapter 5. An increase in EBVps of the litter was associated with decreases in average placental weight and within-litter variation in placental weight, and an increase in average placental efficiency. Average fetal length decreased with increasing EBVps, but weights of liver, adrenals, and small intestine showed relative increases with increasing EBVps. Average serum cortisol concentrations very significantly increased with increasing EBVps, but the other blood characteristics (hematocrit, glucose, fructose, albumin, estradiol-17ß) were not related to EBVps. Glycogen concentrations in liver and longissimus dorsi muscle increased with increasing EBVps, whereas heart glycogen concentration decreased with increasing EBVps. The percentage of carcass fat increased with increasing EBVps. Relationships of relative liver weight, relative small intestinal weight, and liver and muscle glycogen levels with EBVps were solely due to highly elevated serum cortisol levels in litters with high EBVps. The observed differences in fetal development in relation to EBVps suggest a higher degree of physiological maturity in litters with high EBVps. Differences in fetal cortisol accounted for most of the maturational differences. The results imply that selection for improved piglet survival will lead to slightly

smaller piglets that nevertheless have an improved ability to cope with hazards during birth and within the first days of life.

Chapter 6 (General Discussion) first discusses the usefulness of EBVps to study biological backgrounds of genetic differences in piglet survival. It is concluded that EBVps also has predictive value for survival in experimental groups with relatively small numbers of animals. The physiological basis of genetic differences in piglet survival can be investigated in litters that sufficiently differ in EBVps. Furthermore, Chapter 6 discusses the results of Chapter 2 through 5 and concludes that the higher farrowing and postnatal survival rates of litters with high EBVps compared to litters with low EBVps are mainly due to an increased physiological maturity at birth. In this respect, litters with high EBVps show striking similarities with Meishan piglets and piglets from genetically obese lines. Results in this thesis suggest alterations of the hypothalamus-pituitary-adrenal axis (HPA axis) as a consequence of selection for piglet survival. Therefore, Chapter 6 also provides some background information on the function and development of the HPA axis during late gestation in several species, with special emphasis on the pig. The last section of Chapter 6 serves to illustrate that knowledge on biological backgrounds of genetic differences in piglet survival can contribute to our understanding of the consequences of selection in the field. This section also includes some speculation on the possibilities of applying the current knowledge in the field.

General Conclusions

1. The usefulness of EBVps as accurate pedictors for realized survival from end of gestation until weaning has been validated by Knol (2001). This thesis shows that from a population of animals with known EBVps interesting experimental groups can be formed to study the biological backgrounds of genetic differences in piglet survival.

2. Underlying biological mechanisms of genetic differences in piglet survival involve processes or factors that play a role before birth, rather than during or after birth.

3. The very strong relationship between fetal cortisol and EBVps suggests genetically determined differences in the development and(or) maturation of the hypothalamus-pituitary-adrenal (HPA) axis during late gestation.

4. Differences in development and(or) maturation of the HPA axis may influence fetal development and maturation through effects on organ development and glycogen deposition.

5. The biological basis for increased piglet survival with increasing EBVps shows similarities with biological mechanisms that are likely to explain the higher survival rates of Meishan vs. Large White piglets and piglets from genetically obese vs. lean lines. Therefore, results of studies that compare physiological characteristics of Meishan with Large White piglets or genetically obese with lean piglets, will contribute to our understanding of the biological backgrounds of genetic differences in piglet survival within Western breeds.

6. Research on biological aspects of genetic differences in piglet survival contributes to our understanding of the practical consequences of selection for increased piglet survival.

7. The possibility to measure glycogen reserves of newborn piglets by a non-invasive technique such as nuclear magnetic resonance (NMR) offers interesting opportunities to genetically improve piglet survival in situations where large scale registration of individual preweaning piglet survival is not possible.

Samenvatting

Inleiding

Bij de moderne zeug zijn gemiddeld ruim 12 biggen aanwezig in de baarmoeder aan het eind van de dracht. Van deze 12 biggen sterft gemiddeld 20% (ruim twee biggen) in de periode tot spenen.

Het geboorteproces (de partus) is de eerste kritieke gebeurtenis voor een big. Gemiddeld wordt 3-8% van de biggen doodgeboren. De belangrijkste oorzaak van doodgeboorte is verstikking in het geboortekanaal. Verstikking kan optreden als gevolg van verminderde doorbloeding van de placenta door het effect van opeenvolgende baarmoedercontracties, vroegtijdig loslaten van de placenta, of vroegtijdig scheuren van de navelstreng.

De sterfte onder levendgeboren biggen tijdens de zoogperiode varieert van enkele procenten tot wel 30%. De meeste sterfte (50-70%) vindt plaats gedurende de eerste drie dagen na de geboorte, met als belangrijkste oorzaken verhongering en dooddrukken door de zeug.

Geboortegewicht is belangrijk voor overleving. Lichtere biggen hebben een grotere kans om dood geboren te worden. Tevens zijn lichte biggen over het algemeen minder in staat om te concurreren met zwaardere toomgenoten aan de uier voor de opname van biest. Daardoor hebben lichte biggen een hogere kans om te sterven als gevolg van verhongering, onderkoeling, of ziekte. Lichte biggen hebben vooral een verhoogd sterfterisico als ze geboren worden in een grote toom of in een toom met veel variatie in geboortegewicht. Naast geboortegewicht spelen de hoeveelheid energiereserves van een big bij geboorte (bijvoorbeeld glycogeen in lever en spieren) en de mate van rijping van bepaalde vitale organen (longen, maag-darmstelsel) een essentiële rol bij overleving.

De moedereigenschappen van een zeug zijn van groot belang voor de overlevingskansen van haar biggen. Goede moeders worden gekenmerkt door rust, kalmte en voorzichtigheid bij het gaan liggen. Ook reageert een goede moeder op het alarmerende gekrijs van biggen die doodgedrukt dreigen te worden. Daarnaast produceert een goede moeder voldoende biest en melk van goede kwaliteit.

De manier waarop zeugen gehuisvest zijn in de kraamstal speelt een belangrijke rol bij het optreden van biggensterfte. Huisvesting van zeugen in kraamboxen heeft als doel de bewegingsvrijheid van de zeug te beperken om op deze manier biggensterfte door dooddrukken te verminderen. Huisvesten van zeugen in kraamboxen biedt meer mogelijkheden om specifieke voorzieningen voor de biggen te creëren, zoals bijvoorbeeld een verwarmd 'biggen-nest' om de kans op onderkoeling te verminderen. Tenslotte kan bij huisvesting van zeugen in kraamboxen de varkenshouder op een veilige en praktische manier assisteren bij de partus en extra aandacht geven aan zwakke biggen.

Assistentie bij de partus en individuele aandacht voor zwakkere biggen kan de biggensterfte in de kraamstal aanzienlijk verminderen. Echter, door het toenemende aantal zeugen per bedrijf en de hoge kosten voor arbeid in westerse landen is het economisch niet haalbaar om deze vorm van management op grote schaal toe te passen.

De huidige hoge biggensterfte leidt niet alleen tot aanzienlijke economische verliezen, maar is ook uit ethisch oogpunt onaanvaardbaar. Door stijgende worpgroottes als gevolg van genetische selectie komt overleving van biggen in de toekomst nog verder onder druk te staan. Grotere worpen gaan namelijk gepaard met een verlaging van het geboortegewicht en toenemende concurrentie aan de uier. Verder kan de huidige selectie op mager vlees percentage nadelig werken op overleving van biggen. Onderzoek heeft aangetoond dat biggen van genetisch magere zeugen zwakker zijn, omdat ze minder volwassen zijn bij geboorte.

Bovenstaande ontwikkelingen in de varkenshouderij hebben geleid tot het opzetten van een grootschalig onderzoeksproject naar de genetische en biologische achtergronden van biggensterfte. Het genetische gedeelte van dit project heeft reeds aangetoond dat overleving van biggen erfelijk bepaald is en dat het mogelijk is om door middel van genetische selectie de overleving te verbeteren. Bij selectie op overleving worden dieren gekozen op basis van hun geschatte fokwaarde voor overleving. De fokwaarde voor overleving van een big is een schatting van de erfelijke aanleg voor overleving. Om fokwaarden voor overleving te kunnen schatten is informatie nodig over prestaties van bloedverwanten. Daartoe is op grote schaal overleving van biggen geregistreerd. In Tabel 1 zijn fokwaarden voor overleving geschat van de nakomelingen van drachtige zeugen op basis van informatie van 60000 bloedverwanten. De worpen zijn vervolgens ingedeeld in twee groepen: een groep met een

gemiddelde lage fokwaarde voor overleving (-0.76%) en een groep met een gemiddeld hoge fokwaarde voor overleving (+4.21%). Op basis van fokwaarde verwacht je tussen deze groepen een verschil van 4.97% in de overleving van eind dracht tot spenen. Het verschil in werkelijke overleving tussen de twee groepen worpen is 4.7% (83.6% *versus* 78.9%) en komt dus goed overeen met het verwachte verschil. Verschillen in overleving zijn zichtbaar zowel bij de geboorte (partus-overleving) als in de zoogperiode (levendgeb. overleving). Fokwaarden voor overleving blijken dus goede voorspellers te kunnen zijn van werkelijke uitval van eind dracht tot het moment van spenen.

Tabel 1. Werkelijke overleving van een groep worpen met lage en hoge fokwaarden voor overleving

	Fokwaarde overleving 'laag'	Fokwaarde overleving 'hoog'
Aantal worpen	107	108
Gemiddelde fokwaarde, %	-0.76	+4.21
Totale overleving, %	78.9	83.6
Partus-overleving, %	90.7	93.4
Levendgeb. overleving, %	86.7	89.4

Resultaten uit: Knol, E.F. 2001. Genetic aspects of piglet survival. Ph.D. dissertation, Wageningen University.

Doel van dit Proefschrift

Dit proefschrift beschrijft biologische aspecten van erfelijk bepaalde verschillen in big-overleving. Doel van dit proefschrift is het verkrijgen van inzicht in de biologische achtergrond van erfelijk bepaalde verschillen in overleving. Dit kan bijdragen tot een beter begrip van de consequenties van selectie, doordat inzicht wordt verkregen in onderliggende fysiologische processen die kunnen veranderen als gevolg van selectie.

Resultaten

Sinds 1993 wordt op een aantal bedrijven met dieren van de fokkerij-organisatie TOPIGS de overleving van biggen en daarmee samenhangende kenmerken, zoals geboortegewicht, worpgrootte en draagtijd, nauwkeurig geregistreerd. In **hoofdstuk 2** van dit proefschrift is een deel van deze gegevens statistisch geanalyseerd. Het betreft een dataset van bijna 8000 worpen, afkomstig van vier genetisch verschillende lijnen. Doel van de analyses was om te bepalen of er verschillen zijn in doodgeboorte tussen de vier lijnen. Verder zijn relaties van doodgeboorte met verschillende relevante kenmerken geanalyseerd.

Er werden geen significante verschillen gevonden in doodgeboorte tussen de vier lijnen. Het aantal doodgeboren biggen per worp nam toe met afnemende draagtijd, toenemende worpgrootte en afnemend geboortegewicht. Binnen-worp variatie in geboortegewicht bleek niet gerelateerd aan doodgeboorte. Worpen met meer doodgeboren biggen hadden ook meer uitval van levendgeboren biggen.

De afwezigheid van verschillen in doodgeboorte tussen de onderzochte lijnen kan duiden op het ontbreken van onderliggende genetische variatie in doodgeboorte tussen lijnen. Uiteraard hoeft dit niet te betekenen dat er geen genetische variatie in doodgeboorte is binnen lijnen. Het feit dat worpen met doodgeboren biggen ook meer sterfte van levendgeboren biggen hadden, kan duiden op een algemeen verlaagde levensvatbaarheid van dit soort worpen.

In **hoofdstuk 3** is op een TOPIGS-bedrijf bij ruim 300 worpen met geschatte fokwaarden voor overleving gekeken naar sterfte rondom de partus. Doel van deze studie was om te bepalen of groepen dieren die verschillen in erfelijke aanleg voor overleving verschillen vertonen in de hoeveelheid en in het moment van sterfte rondom de partus. Door

sectie kon bij iedere dode big het moment van sterfte ten opzichte van het moment van partus worden vastgesteld.

De totale sterfte tot ongeveer 12 uur na partus (inclusief doodgeboorte) nam significant af met toenemende fokwaarde voor overleving van de worp. Het aantal biggen per worp dat stierf vóór en tijdens de partus bleek significant af te nemen met toenemende fokwaarde voor overleving van de worp. Daarentegen was de sterfte direct (enkele minuten) na de partus en sterfte van levendgeboren biggen in de eerste 12 uur niet gerelateerd aan fokwaarde voor overleving van de worp. De significante afname in de sterfte vóór en tijdens de partus in relatie tot fokwaarde voor overleving kon niet verklaard worden door verschillen in geboortegewicht van de dode biggen.

Het verloop van de partus is van grote invloed op overleving en vitaliteit van biggen. Vanwege een groter risico op verstikking tijdens de partus, neemt de kans op doodgeboorte toe met toenemende partusduur en toenemende tussenbigtijd (tijdsinterval tussen de geboorte van twee biggen). Zuurstofgebrek tijdens de partus vermindert ook de overlevingskansen van levendgeboren biggen. Biggen die ernstig zuurstofgebrek hebben gehad tijdens de partus zijn minder vitaal en nemen minder snel biest op. Een snelle opname van biest is van levensbelang, zowel als energievoorziening, maar ook voor het verkrijgen van de nodige antistoffen. In **hoofdstuk 4** is onderzocht of het verloop van de partus (duur en tussenbigtijd) en het gedrag van biggen direct na geboorte gerelateerd zijn aan de erfelijke aanleg voor overleving. Het gedrag van biggen werd gemeten door te registreren hoe lang het duurt vanaf de geboorte tot de big voor het eerst rechtop staat, bij de uier is, een speen in de mond heeft en biest drinkt. De waarnemingen werden verricht aan 25 tomen waarvan de biggen allemaal een geschatte fokwaarde voor overleving hadden.

De kans op doodgeboorte en sterfte gedurende de eerste drie dagen na partus nam significant af met toenemende fokwaarde voor overleving. Echter, het verloop van de partus en het gedrag van biggen was niet gerelateerd aan de fokwaarde voor overleving. Concluderend hieruit kunnen we stellen dat de betere overleving van biggen met een hoge erfelijke aanleg voor overleving in vergelijking met biggen met een lage erfelijke aanleg voor overleving blijkbaar niet veroorzaakt wordt door verschillen in partusverloop of gedrag direct na geboorte.

Uit het voorgaande kunnen we concluderen dat de biologische achtergrond van erfelijk bepaalde verschillen in overleving waarschijnlijk niet gezocht moet worden in processen tijdens of na de geboorte. Daarom zijn in **hoofdstuk 5** aspecten van laat-foetale ontwikkeling, waarvan verondersteld wordt dat ze gerelateerd zijn aan de kans op overleving, nader onderzocht. Voorbeelden van dit soort aspecten zijn onder andere de ontwikkeling van de placenta, de ontwikkeling van organen en de hoeveelheid energiereserves bij geboorte. Voor dit onderzoek zijn 46 drachtige zeugen gebruikt, waarvan de biggen in de baarmoeder een geschatte fokwaarde hadden voor overleving. De biggen werden door middel van keizersneden op dag 111 van de dracht (gemiddelde duur van de dracht is 114 dagen) uit de baarmoeder verwijderd. Vervolgens is van elke big een bloedmonster genomen, organen zijn verwijderd en gewogen en energiereserves (glycogeen en vet) zijn bepaald. Van iedere big is ook de placenta gewogen. Het doel van deze studie was om te bepalen of de mate van ontwikkeling van biggen tijdens de late dracht verschillend was tussen worpen die verschillen in erfelijke aanleg voor overleving.

Worpen met een hoge fokwaarde voor overleving bleken gemiddeld lichtere placenta's te hebben dan worpen met een lage fokwaarde voor overleving. Ook was de variatie in placentagewicht lager in worpen met een hoge fokwaarde voor overleving. Biggen uit worpen met een hoge fokwaarde voor overleving hadden een relatief zwaardere maag en dunne darm dan biggen uit worpen met een lage fokwaarde voor overleving. Dit is een aanwijzing dat het maag-darmstelsel van biggen met een hoge fokwaarde voor overleving verder ontwikkeld is aan het eind van de dracht, hetgeen consequenties kan hebben voor de efficiëntie van opname en vertering van nutriënten na de geboorte. Het glycogeengehalte in de lever en spieren en het vetpercentage in het karkas nam significant toe met toenemende fokwaarde voor overleving. Glycogeen in lever en spieren is direct na de geboorte van essentieel belang voor het op peil houden van de bloedglucose spiegel en voor warmteproductie. De gevonden relaties van lever- en spierglycogeen met fokwaarde voor overleving betekenen derhalve dat biggen met een hoge fokwaarde voor overleving beter in staat zijn om na de geboorte hun glucosegehalte op peil te houden en warmte te produceren. Daarnaast zou het hogere vetpercentage van biggen met een hoge fokwaarde kunnen bijdragen aan een betere isolatie tegen kou direct na de geboorte.

Het meest opvallende resultaat van het experiment in hoofdstuk 5 is de aanzienlijk hogere cortisolconcentraties in het bloed van biggen met een hoge fokwaarde voor overleving. Dit is zeer interessant, aangezien cortisol vóór de geboorte een essentiële rol

speelt bij de ontwikkeling en rijping van organen die de overlevingskansen van de big tijdens en na de geboorte beïnvloeden. Cortisol bevordert bijvoorbeeld de ontwikkeling en rijping van de longen, lever, maag, dunne darm, nieren en hersenen. Ook stimuleert cortisol de aanmaak van glycogeen in lever en spieren. De gevonden verschillen in maag-darmontwikkeling en hoeveelheid lever- en spierglycogeen in relatie tot fokwaarde voor overleving konden dan ook volledig worden verklaard door verschillen in cortisolniveaus tussen biggen met verschillende fokwaarden voor overleving.

Concluderend uit hoofdstuk 5 kunnen we stellen dat biggen die verschillen in erfelijke aanleg voor overleving duidelijke verschillen vertonen in laat-foetale ontwikkeling. De verschillen in cortisol en daarmee samenhangende verschillen in orgaan-ontwikkeling en hoeveelheid energiereserves duiden er op dat biggen met een hoge erfelijke aanleg voor overleving rijper en meer ontwikkeld zijn aan het eind van de dracht.

Algemene Discussie

De eerste paragraaf van **hoofdstuk 6** (algemene discussie) bediscussieert de bruikbaarheid van fokwaarden voor overleving voor onderzoek naar de biologische achtergrond van erfelijk bepaalde verschillen in overleving. Er wordt geconcludeerd dat relatief kleine aantallen worpen met voldoende contrast in fokwaarde interessante experimentele groepen vormen om de biologische achtergrond van erfelijk bepaalde verschillen in overleving te onderzoeken.

Vervolgens zijn de resultaten uit hoofdstuk 2 tot en met 5 gecombineerd om een totaalbeeld te schetsen van de huidige kennis omtrent de biologische achtergrond van erfelijk bepaalde verschillen in overleving. De verschillen in doodgeboorte en sterfte van levendgeboren biggen in relatie tot erfelijke aanleg voor overleving lijken voornamelijk te worden veroorzaakt door verschillen in foetale ontwikkeling en rijping aan het eind van de dracht. In dit opzicht lijken biggen met een hoge fokwaarde voor overleving sterk op Meishan biggen en biggen van genetisch vette lijnen. Meishan biggen en biggen van genetisch vette lijnen zijn, ondanks hun lage geboortegewicht, zeer vitaal. Dat lijkt verklaard te kunnen worden door een hogere mate van ontwikkeling of rijpheid bij geboorte in vergelijking tot biggen van westerse rassen en genetisch magere lijnen.

Hoofdstuk 6 besteedt verder uitgebreid aandacht aan de ontwikkeling en maturatie van de hypothalamus-hypofyse-bijnier as in de laatste fase van de dracht bij diverse zoogdieren,

met speciale aandacht voor het varken. De grote verschillen in cortisolgehaltes tussen worpen met verschillende fokwaarden voor overleving duiden namelijk op erfelijk bepaalde verschillen in ontwikkeling en/of maturatie van de hypothalamus-hypofyse-bijnier as.

Afsluitend in hoofdstuk 6 wordt het belang en de toepasbaarheid van de huidige resultaten voor de praktijk besproken. De huidige kennis van biologische aspecten van erfelijk bepaalde verschillen in overleving bevordert het begrip van de gevolgen van selectie op overleving. Op basis van de resultaten in dit proefschrift worden enkele biologische kenmerken besproken die als alternatief kunnen dienen voor selectie op basis van fokwaarden. Non-invasieve technieken om glycogeen direct na de geboorte te bepalen bieden interessante perspectieven om genetische vooruitgang in overleving te realiseren in de veelvoorkomende situatie waarin fokwaarden voor overleving niet geschat kunnen worden.

Algemene Conclusies

1. De bruikbaarheid van fokwaarden als voorspellers voor werkelijke overleving van eind van de dracht tot spenen is reeds aangetoond door Knol (2001)[1]. Dit proefschrift laat zien dat uit een populatie dieren met geschatte fokwaarden voor overleving interessante experimentele groepen gevormd kunnen worden om de biologische achtergrond van erfelijk bepaalde verschillen in overleving te onderzoeken.

2. De biologische achtergrond van erfelijk bepaalde verschillen in overleving moet vooral gezocht worden in processen of factoren die een rol spelen vóór de geboorte in plaats van tijdens of na de geboorte.

3. Het overtuigende, positieve verband tussen foetale cortisol gehaltes aan het eind van de dracht en fokwaarde voor overleving wijst op erfelijk bepaalde verschillen in de ontwikkeling en/of maturatie van de hypothalamus-hypofyse-bijnier as aan het eind van de dracht.

4. Verschillen in de ontwikkeling en/of maturatie van de hypothalamus-hypofyse-bijnier as beïnvloeden foetale ontwikkeling en rijping via effecten op orgaanontwikkeling en glycogeenvorming.

5. Biggen met een hoge fokwaarde voor overleving vertonen aan het eind van de dracht sterke fysiologische overeenkomsten met Meishan biggen en biggen van lijnen die

[1]Knol, E.F. 2001. Genetic aspects of piglet survival. Ph.D. dissertation, Wageningen University.

geselecteerd zijn op vetaanzet.

Het ligt daarom voor de hand dat de hogere overleving van biggen met hoge *versus* lage fokwaarde verklaard kan worden door onderliggende fysiologische processen die eveneens een rol spelen bij de hogere overleving van Meishan *versus* westerse rassen en genetisch vette *versus* genetisch magere lijnen.

6. Onderzoek naar de biologische achtergrond van erfelijk bepaalde verschillen in overleving draagt bij aan een beter begrip van de consequenties van selectie op overleving in de praktijk.

7. De mogelijkheid om glycogeenreserves van pasgeboren biggen te meten met behulp van non-invasieve technieken, zoals Nuclear Magnetic Resonance (NMR) biedt interessante mogelijkheden om te selecteren op overleving in situaties waarin fokwaarden niet geschat kunnen worden.

Curriculum Vitae

Jascha Iri Leenhouwers werd op 27 augustus 1971 geboren te Oostburg. In 1989 behaalde hij het VWO diploma aan Scholengemeenschap 't Zwin te Oostburg. In hetzelfde jaar begon hij met de studie Biologie aan de Landbouwuniversiteit te Wageningen. Na het behalen van de propaedeuse koos hij voor de oriëntatie Organisme. Zijn eerste afstudeervak heeft hij gedaan bij de leerstoelgroep Fysiologie van Mens en Dier te Wageningen, waar hij de effecten van nitraat op de jodide-opname door de schildklier bij ratten heeft onderzocht. Het tweede afstudeervak betrof een studie naar fysiologische aspecten van stress bij de Afrikaanse meerval en werd uitgevoerd bij de leerstoelgroepen Ethologie en Visteelt en Visserij te Wageningen. Zijn derde afstudeervak heeft hij in de Verenigde Staten uitgevoerd, bij het Department of Pharmacology and Therapeutics van het Louisiana State University Medical Center te Shreveport, LA. Hij deed daar onderzoek naar de effecten van interferon-α op cognitieve en motorische processen bij de rat. In 1995 studeerde hij af, waarna hij in 1996 bij de leerstoelgroep Fokkerij en Genetica aan het promotieonderzoek begon zoals beschreven staat in dit proefschrift.

Sinds 1 november 2001 is hij tijdelijk werkzaam als onderzoeker bij het Institute for Pig Genetics (IPG) te Beuningen.

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