

Uterine capacity in the pig reflects a combination of uterine environment and conceptus genotype effects^{1,2}

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ABSTRACT: Prenatal losses in U.S. pig breeds range from 30 to 50%, of which greater than 75% occurs before d 30 of gestation and is thought to result from littermate asynchrony. Numbers of embryos can be experimentally increased to d 30 using superovulation (excess ova shed) and superinduction (transfer of embryos to an already pregnant uterus); however, these females farrow the same number of pigs as untreated controls. These data demonstrate that between d 30 and parturition there are significant additional periods of conceptus loss, which has led to the conclusion that uterine capacity (i.e., the number of conceptuses a sow uterus can accommodate) is the major limitation to litter size in the pig. The special importance of uterine capacity in the pig may result from the noninvasive epitheliochorial type of placentation in this species, making the surface area of attachment between the placenta and endometrium a limiting factor. In devising selection schemes for this trait, one could logically conclude the

selection for either longer uterine horns or for a reduced conceptus size should potentially increase litter size in the pig. Researchers have evaluated the impact of differences in prepubertal uterine horn length on subsequent uterine capacity using a unilateral hysterectomy-ovariectomy model but have had modest and variable success in increasing litter size at farrowing. In contrast, results from our laboratory suggest that placental size is moderately heritable and results in consistent increases in litter size of two to three pigs in the Yorkshire breed with little impact on pig birth weight or neonatal viability. This selection of pigs for smaller and relatively more efficient placentae (i.e., the number of grams of fetus that can be supported by 1 g of placenta) seems to provide a useful method for increasing litter size in the pig. A careful evaluation of the physiologic and genetic differences of conceptuses with differing placental efficiencies is necessary if we are to determine specific factors affecting litter size in the pig.

Key Words: Litter Size, Placenta

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Introduction

Uterine capacity is defined as the number of conceptuses that the pig uterus can successfully carry to term. Data suggest that limitations of uterine capacity are set early in gestation, possibly around the time of conceptus elongation on d 11 through 13 (Figure 1). It is during this time that the conceptus begins to

produce and secrete significant amounts of estrogen into the uterine lumen, which results in endometrial secretion of a myriad of growth factors such as IGF-I, which could affect subsequent uterine as well as conceptus growth and development (Wilson and Ford, 1997). At this time, littermate conceptuses space evenly throughout the uterus (Dhindsa et al., 1967; Dziuk, 1968, 1985) and expand asynchronously from 1-cm spherical blastocysts to filamentous forms of variable length (Geisert et al., 1982), in association with a 20 to 30% conceptus loss in U.S. and European pig breeds (Dziuk, 1968, 1987; Pope, 1994). Uterine capacity begins to measurably affect litter size after d 30 of gestation in the pig (Fenton et al., 1972; Pope et al., '971; Huang et al., 1987), when a real competition for limited uterine space and nutrients by littermates becomes increasingly critical.

Uterine capacity can be defined in terms of the relative surface area of placental endometrial attachment required to support the nutrient requirements of an individual fetus throughout gestation. Recent evidence suggests that placental efficiency (**PE**; fetal wt/

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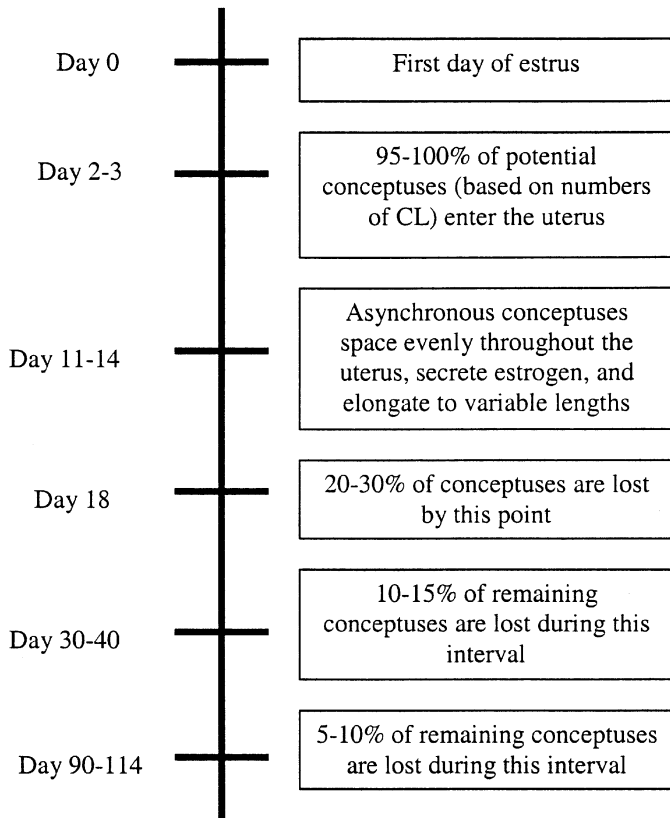


Figure 1. A time line demonstrating the time periods of conceptus loss in the pig.

placental wt) is an individual conceptus trait and is highly variable within a litter (Wilson et al., 1999). Impacts of selection for uterine length (Christenson et al., 1990), ovulation rate (Johnson et al., 1999), and placental efficiency (Wilson et al., 1999) have shown variable success in increasing litter size. In this paper, we will attempt to summarize the various approaches used to increase uterine capacity, both from the maternal and fetal sides, and the impacts they have had on litter size.

Genetic Selection

Johnson and co-workers at the University of Nebraska have used genetic selection in an attempt to increase litter size in the pig, but with limited success. Johnson et al. (1999) conducted 11 generations of selection (from a Large White and Landrace genetic base) for increased index of ovulation rate followed by three generations of selection for litter size. By the 11th generation of selection they verified a selection advantage of 7.4 ovulations and 3.3 fetuses on d 50 but only realized an advantage of 1.1 live pigs at farrowing. The response to selection at generation 14 was an increase of 1.4 live pigs/litter; however, the number of stillborn pigs increased and pig birth weights decreased. As a result, the number of pigs weaned actually declined in the selected line compared to the con-

trol line. The authors speculated that as ovulation rate increased in the selection line uterine capacity increasingly became the limiting factor in prenatal survival after d 50 of gestation. The authors went on to speculate that selection on component traits of litter size would have been more effective if in addition to ovulation rate a measure of uterine capacity had also been included, as previously suggested by Bennett and Leymaster (1989).

Cassady et al. (2001) attempted to identify chromosomal regions harboring QTL for reproductive traits in pigs using a reference population created by Rathje et al. (1997) at the University of Nebraska. Grandparents of this population had been selected for ovulation rate and embryonic survival. While reporting evidence for QTL for a number of reproductive traits (including ovulation rate, age at puberty, number of teats, and number of fully formed pigs) he concluded that few, if any, major genes for reproductive traits were segregating in the population. He went on to conclude that little evidence exists to encourage marker-assisted selection at the present time.

This conclusion is consistent with results recently reported by Linville et al. (2001), who used the candidate gene approach to determine whether specific loci explain the observed differences in litter size. They found no associations between six polymorphic markers in two lines of pigs, again originating from the selected and control lines described by Johnson et al. (1999). In fact, for several of these markers, the estimated effect of purported favorable alleles was negative. They reported that these selection lines exceeded the control line by 20 to 50% in both ovulation rate and litter size. The authors went on to explain the rationale for the selection of the six specific markers chosen, on an individual basis, but, as Cassady et al. (2001) concluded for this same population, selection for ovulation rate, embryonic survival, and litter size seems to have acted on multiple loci, each of which exerts only a modest effect (i.e., these are polygenic traits). Although there are many possible reasons for this lack of association reported by Linville et al. (2001) between selected markers and litter size, a failure to understand what specific physiologic differences were selected for in this population suggests that little progress should be expected using only this approach. In the next section, we will discuss the findings of several researchers who are attempting to understand the necessary interactions between the conceptus and the uterus that promote optimal conceptus survival through alteration of uterine capacity.

Conceptus-Uterine Interaction

Evidence suggesting that uterine capacity is limiting to litter size after d 30 of gestation is based largely on studies using superovulation (excess number of ova shed), superinduction (transfer of embryos to an already pregnant uterus), and unilateral hyster-

ectomy-ovariectomy (UHO) models. Superovulation and superinduction increase the number of conceptuses surviving to d 30 (percentage of embryo survival is similar); however, these females do not farrow litters larger than controls (Fenton et al., 1972; Monk and Erb, 1974; Webel and Dziuk, 1974). Females subjected to UHO ovulate normal numbers of ova, but only farrow approximately one-half the number of pigs of intact controls (Christenson et al., 1987). The UHO model has been used to estimate uterine capacity per uterine horn in the absence of any possible limitation in ovulation rate (Christenson et al., 1987). In these studies, it was concluded that UHO gilts that had the largest litters ($> 1/2$ of control gilts) at farrowing may provide the most optimal uterine environment (i.e., increased uterine capacity). Following this rationale, Gama and Johnson (1993) used UHO in lines of gilts at the University of Nebraska that had been selected for differences in ovulation rate, embryo survival to d 50, and litter size. Pregnant gilts were slaughtered on d 93 through 100 of gestation and ovulation rate, number of fully formed pigs, and number of mummied pigs were determined. As previously reported by Christenson et al. (1987), uterine capacity was estimated as twice the number of fully formed fetuses in the remaining horn. When this was accomplished, the estimated difference between individuals selected for increased litter size and the randomly selected controls was 0.66 ± 1.28 pig. Although this increase was not significant, the authors suggested that these data indicate that additive genetic variance for uterine capacity does exist in swine.

In the pig, uterine capacity may specifically relate to epitheliochorial and diffuse placentation, whereby the chorionic epithelium is in direct contact with the uterine luminal epithelium (Grosser, 1933; Benirschke, 1983; MacDonald and Bosma, 1985). This placental type, which is appositional rather than invasive and relies largely on simple diffusion, requires an adequate surface area for nutrient exchange from the maternal to fetal blood streams. Between d 20 and 30 of gestation, there is a rapid increase in placental length that slows asymptotically, reaching a plateau around d 70 before increasing again after d 100 (Pomeroy, 1960; Knight et al., 1977). From d 30 to 40, the placenta progresses from a very simply organized structure, consisting of a thin membrane, hyaluronic acid gel, and a rapidly proliferating system of blood vessels to a more complex structure (Perry, 1981; Bazer, 1989). Also between d 30 and 35 of gestation, the yolk sac rapidly regresses, and the responsibility for the absorption of oxygen and nutrients and the removal of carbon dioxide and waste is shifted to the highly vascularized chorioallantoic membrane (Bjørkman, 1973; Tiedemann and Minuth, 1980; Dantzer, 1985).

Placental capillaries ramify throughout the entire surface of the placenta in close contact with the chorionic epithelium, except for the ends, which are nonvascular and are referred to as necrotic tips (Patten,

1948). From d 35 to 70 of gestation, the surface area of the chorioallantoic membrane increases rapidly (Knight et al., 1977). This results from the prolific folding of the placental surface into permanent folds in the endometrium, followed by the development of an interlocking network of placental and endometrial microvilli, which function to further expand the placental:endometrial surface area of exchange (Friess et al., 1980; Bjørkman and Dantzer, 1987). From d 70 through approximately d 90 there is little noticeable change in placental surface area (Knight et al., 1977), but from d 90 of gestation through term as much as a doubling of placental surface area is seen (Wigmore and Strickland, 1985; Biensen et al., 1998).

As previously stated, the limitations of uterine capacity begin to affect conceptus survival after d 30 and are associated on d 35 to 40 with a marked and abrupt increase in the surface area of placental exchange due to the development of microscopic interdigitations between the placenta and uterine luminal surface referred to as primary rugae (Bjørkman and Dantzer, 1987; Leiser and Dantzer, 1988; Leiser and Dantzer, 1994). During the last third of gestation, when another period of observed fetal loss occurs (Christenson et al., 1987; Johnson et al., 1999), the functional surface area for nutrient and waste product exchange is again accelerated in association with rapid fetal growth by the development of secondary rugae, an additional tier of interdigitation along the primary rugae (Friess et al., 1980; Bjørkman and Dantzer, 1987).

In addition to the progressive increases in the functional placental:endometrial surface area allowing fetal-maternal exchange, the vascularity of placental and adjacent endometrial tissues also changes with the advancement of gestation, in conjunction with a progressive decrease in the diffusion distance between the placental and fetal capillaries. Vonnahme et al. (2001) demonstrated that in the white composite breeds, density of placental blood vessels per unit surface area tissue (vascular density) actually decreased during the first rapid expansion of the placenta from d 25 through 44, then increased progressively from d 44 through 90 before reaching a plateau until term (Figure 2). Of interest is the fact that vascular density did not increase during either the early or late periods of increased fetal death. Further, Vallet et al. (1996) and Pearson et al. (1998) have suggested that fetal erythropoiesis is negatively affected by intrauterine crowding and may play a role in fetal loss. Vonnahme et al. (2001) also reported that placental vascular endothelial growth factor (VEGF), a potent angiogenic and permeability-enhancing factor, followed the same pattern as that of placental vascular density throughout gestation and was positively correlated with both placental ($r = 0.34$; $P < 0.05$) and adjacent endometrial ($r = 0.34$; $P < 0.05$) vascular density changes of individual placentae (see Vonnahme et al., 2001 for technical details). Increased permeability at the placental:endometrial interface with advancing gestation was sug-

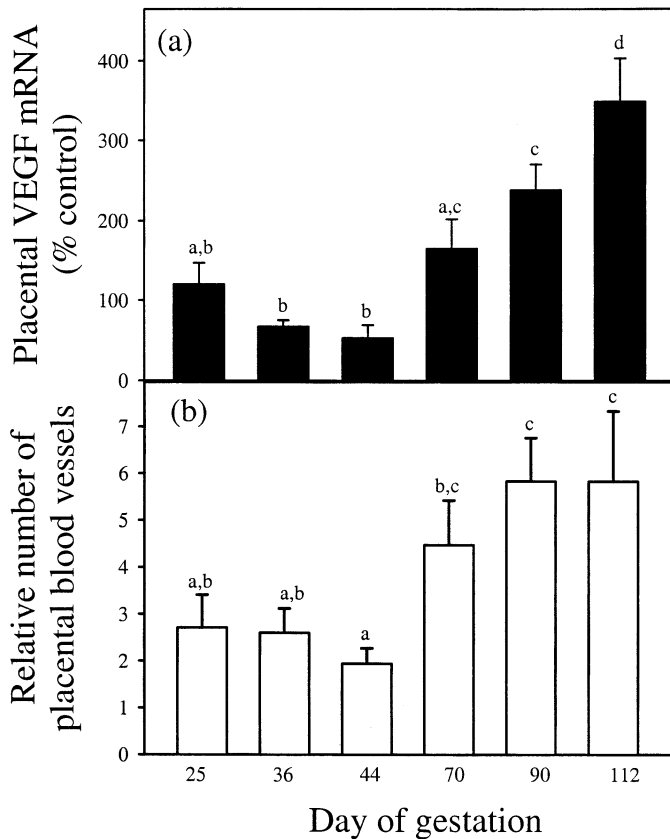


Figure 2. (a) Changes in vascular endothelial growth factor mRNA and (b) the relative number of blood vessels per unit area of placental tissue throughout gestation in the pig. Means and SEM with different superscripts within a measurement differ ($P < 0.05$) (reproduced with permission from Vonnahme et al., 2001).

gested by Friess et al. (1980, 1982), who demonstrated that the functional maternal:fetal intercapillary distance decreased from 15 to 20 μm to approximately 2 μm with the advancement of gestation.

In the pig, placental transfer of freely diffusable nutrients seems to rely on a vascular anatomy that is either concurrent or possibly crosscurrent (Friess et al., 1982). Transported solutes such as glucose, amino acids, ions such as sodium, potassium, calcium, and protons require transporter protein-mediated transfer (Sibley et al., 1997). In the pig, this transporter-mediated transfer seems to be concentrated in the troughs of the chorionic folds, which are adjacent to the ridges of endometrial folds, and is generally not tied directly to the rate of blood flow (Friess et al., 1980; Poston, 1997; Sibley et al., 1997). In addition to the transfer that occurs across the uterine luminal epithelial-chorionic epithelial interface, there is also transfer of large macromolecules such as uteroferrin, which are produced by the uterine glands and then absorbed intact by the placental areolae (Perry, 1981; Friess et al., 1982; Roberts et al., 1986; Leiser and Dantzer, 1994). All of these transfer mechanisms are, however,

dependent on an adequate surface area of functional contact between the placenta and uterine wall if the fetus is to exhibit optimal growth and development.

Placental Efficiency

To avoid the confounding effects of differences in ovulation rate and uterine length, both of which have been reported to have impacts on litter size, we chose to compare and contrast the reproductive physiology of the prolific Chinese Meishan gilt (two to five postpubertal estrous cycles) with Yorkshire gilts of similar reproductive age. Although Meishan and Yorkshire gilts at this reproductive age exhibit similar ovulation rates (16.5 ± 5 and 16.3 ± 0.4 , respectively) and uterine lengths, the litter size of Meishan gilts was markedly greater (12.3 ± 0.4 vs 8.9 ± 0.4 live pigs/litter; Ford, 1997). Further, the Meishan and Yorkshire gilts in our herds ovulated at the same time after the initiation of estrous activity, as evidenced by the recovery of embryos at similar stages 48 to 54 h after estrus onset (one to eight-cell embryos). From d 5 to 12 of gestation, however, Meishan conceptuses are smaller than Yorkshire conceptuses due to a selective reduction in the number of trophoblast cells, the cell type containing the rate-limiting enzyme for conceptus estrogen synthesis (Youngs et al., 1993; Rivera et al., 1996; Wilson and Ford, 1997). Further, we observed that although both Meishan and Yorkshire conceptuses initiated estrogen secretion and elongated on the same days of gestation (d 11 to 12), Meishan conceptuses secreted less estrogen into uterine luminal fluid and were smaller (Anderson et al., 1993). The decreased uterine luminal estrogen concentrations in Meishan vs Yorkshire females on d 11 to 12 was associated with reduced levels of total protein, calcium, oxytocin, and IGF-I in the same fluid (Ford and Youngs, 1993; Wilson and Ford, 1997; Vallet et al., 1998). This is consistent with the role of IGF-I in increasing trophoblast mitotic rate in pig conceptuses (Lewis et al., 1992). As a result, Meishan filamentous conceptuses were shorter and contained fewer cells than Yorkshire conceptuses on d 14 (Wilson et al., 1995). Further, Meishan conceptuses exhibit markedly smaller placentae on d 30, 50, 70, 90, and 110 and at term (Hunter et al., 1994; Biensen et al., 1998; Wilson et al., 1998) than do conceptuses of a variety of less-prolific pig breeds. This reduced placental size of the Meishan regardless of the number of conceptuses present seems to be a direct result of a reduced preimplantation uterine exposure to estrogen. Injections of estrogen into pregnant Meishan females around the time of conceptus elongation was found to markedly increase placental size at term (Wilson and Ford, 2000).

The real breakthrough in our understanding of how the Meishan fetus survived on such a tiny placenta came when both Meishan and Yorkshire embryos were placed in the uterus of a Yorkshire recipient female on d 2 and allowed to compete for survival (Wilson et



Figure 3. Similar-sized Meishan and Yorkshire littermates farrowed by a Yorkshire sow.

al., 1998). At farrowing, the umbilical cord of each pig was double-ligated and tagged so that all pigs could be matched with their placentae when they were expelled en masse after all pigs were farrowed. To our surprise, Meishan ($n = 7$) and Yorkshire ($n = 7$) pigs exhibited similar birth weights ($1,308 \pm 76$ and $1,585 \pm 95$ g, respectively), as a result of marked increases in Meishan pig birth weight compared to those farrowed normally by straightbred Meishan females, which average ~ 800 to 900 g (Figure 3). Further, all Meishan pigs were gestated on very small and highly vascular placentae, and all their Yorkshire littermates were gestated on much larger and less-vascular placentae (209 ± 17 and 472 ± 46 g, respectively). At this point we began employing PE as describing the grams of fetus that could be supported by a gram of placenta, as previously used by others (Molton et al., 1978; Kurz et al., 1999). Placental efficiency of Meishan pigs in the litter averaged 6.25, and the PE of their Yorkshire littermates averaged 3.36. These PE differences result from a 56% difference in placental weights and a 17% difference in pig weight. These data confirm that the PE is an individual conceptus trait independent of uterine environmental control. In subsequent studies, we determined that changes in PE were a result of changes in placental weight, not pig weight. Further, there was much less variation in the weights and vascularity of the Meishan placentae within a litter than exhibited by their littermate Yorkshire placentae (S. P. Ford, unpublished observations). Thus, we speculated that during the domestication of the Meishan breed, which encompassed as many as 7,000 yr (Yun, 1988), an intense selection for litter size may have resulted in an indirect selection for small, highly vascular, and relatively uniform placentae. If this was indeed the case, then we felt that there might be significant variation in this trait in our Yorkshire population.

In a subsequent study (Wilson et al., 1999) using our Yorkshire population, pigs were matched to their placentae as described above, and we found that there was significant (threefold) variation in placental weights across females, with as much as twofold differences exhibited within a single litter. From these litters we then selected boars and gilts with birth weights $\geq 1,250$ g that had higher than average PE and those that had lower than average PE. Although pig birth weights of the high-PE group were similar to those of the low-PE group, their placentae were markedly smaller and more vascular. We then allowed these pigs to reach puberty and at the second estrus we bred gilts of each group (high PE or low PE) to boars of the same group and collected farrowing data from parities 1 and 2. In both parities, the high-PE females farrowed more ($P < 0.05$) live pigs than the low-PE group (12.5 ± 0.7 vs 9.6 ± 0.5). Although the high-PE group farrowed pigs that were about 20% lighter than the low-PE group (1.2 ± 0.1 vs 1.5 ± 0.1 kg, $P < 0.05$), their placentae were 40% lighter (250 ± 10 vs 347 ± 15 g, $P < 0.01$), resulting in an increased PE for pigs farrowed in the high-PE group. Interestingly, Vonnahme and Ford (2001) recently reported that selection of Yorkshire pigs for high PE markedly increased placental VEGF mRNA compared to unselected controls. Also of interest was the fact that numbers of stillborn pigs and postfarrowing death losses were low and similar for both groups, suggesting no negative impact on pig viability. Further, when the association between a pig's PE at birth was compared to subsequent production traits in a commercial herd of Yorkshire and Landrace females, no effect of PE was seen on 21-d weight, days to 105 kg, backfat depth, or loin muscle area (Biensen et al., 1999). These data suggest that the selection for PE might be a valuable tool for increasing litter size in commercially relevant pig breeds without decreasing periparturient pig viability.

Validation of the Impacts of Ovulation Rate, Uterine Size, and PE in a Commercial Swine Herd

In a recent study (Wilson et al., 2000), we used a very large, highly productive (average litter size 10.4 pigs/litter), and healthy herd in Iowa (Dayton Pork, Dayton, Iowa; a portion of Swine Graphics Enterprises, Inc., Webster City, IA) to gain insight into the factors that limit litter size in commercial swine production. For too long, researchers have used a few university herds for their studies on litter size without comparing physiological differences in reproductive function (i.e., ovulation rate, uterine length, placental size, etc.) of their herds to those used by the swine industry, or for that matter other university herds. Thus, many of the conclusions drawn from these studies may have limited relevance to today's swine industry. In our attempt to understand the factors limiting litter size, researchers have focused on three main

traits: 1) ovulation rate, 2) uterine size, and, more recently, 3) placental efficiency. Although all three seem moderately heritable, selection for increases in ovulation rate and uterine length have resulted in very limited and highly variable increases in litter size, whereas recent and limited studies using selection for placental efficiency have shown a much greater effect.

For this study (Wilson et al., 2000), a total of 190 Camborough line 6-02 (PIC) sows representing parities 1 to 14 were slaughtered on d 25 ($n = 63$), 36 ($n = 60$), or 44 ($n = 67$) of gestation, and the gravid uteri and associated ovaries were recovered. Uterine length and the number of ovulations were not different among the three groups, averaging 434 cm and 26.6, respectively. Further, there was no correlation between uterine length or ovulation rate and the parity of the sow. Viable conceptus number decreased from 15.8 on d 25 (before the limitations of uterine capacity) to 12.9 on d 36 (after the impact of uterine capacity), then remained relatively constant through d 44 (12.1 fetuses). This reduction in the number of viable conceptuses under the limitation of uterine capacity was reflected by a marked decrease in conceptus survival (number of conceptuses/number of corpora lutea), which decreased from 60.2% on d 25 to 50.1% on d 36.

Although ovulation rate was highly and positively correlated ($P < 0.01$) with the numbers of conceptuses present on d 25 ($r = + 0.50$) before the limitations of uterine capacity were seen, by d 36 this association was lost ($r = + 0.02$; $P > 0.10$). In contrast, length of uterine horns was not associated with the numbers of conceptuses found on d 25 ($r = -0.03$; $P > 0.10$), but these traits were positively correlated ($P < 0.01$) thereafter (d 36, $r = + 0.36$; d 44, $r = + 0.40$). Interestingly, although fetal weight was not associated with conceptus number on any of the days examined, placental weight was negatively correlated ($r = -0.32$; $P < 0.01$) with the number of viable conceptuses on all 3 d examined. We have previously shown (Biensen et al., 1998) that placental weight is highly correlated ($r = + 0.82$; $P < 0.001$) with placental surface area, regardless of breed, sex, or day of gestation, and therefore is a good indicator of placental size.

These data suggest that larger litters on d 25, 36, and 44 are composed of conceptuses exhibiting fetuses of similar size, but with smaller placentae and thus exhibiting an increased PE. Further, the ovulation rate of sows from this commercial herd was extremely high compared to that reported by investigators for their research herds (Christenson, 1993; Ford, 1997; Johnson et al., 1999) but was similar to that reported by Foxcroft (1997) for another line of commercial sows. Additionally, although conceptus number was positively related to ovulation rate on d 25, by d 36 the limitations of uterine size began to reduce conceptus number regardless of ovulation rate. These data suggest that ovulation rate was not a limiting factor for litter size in this large group of commercial sows.

Based on the data reported here for this highly productive commercial herd, it is imperative that we define the reproductive phenotypes of our research herds to make sure that the conclusions we draw are relevant to the industry. This is especially critical in the use of the candidate gene approach, which is being increasingly promoted for the determination of whether specific loci contribute to an increased litter size.

Implications

Data presented in this review suggest that more than adequate numbers of viable embryos enter the uterus on d 2 or 3 of gestation, but due to an asynchrony of development, 20 to 30% of conceptuses are lost by d 18. Additional periods of conceptus loss occur between d 30 and 40 (15 to 20% loss) and during the last third of gestation (5 to 10%) as the competition for limited uterine space becomes critical (i.e., uterine capacity). Uterine capacity seems to be increased by increasing uterine size (maternal effect), or alternatively by decreasing placental size, with a corresponding increase in placental efficiency (individual conceptus effect). If an optimal litter size is to be achieved, future research must concentrate on the selection for reproductive phenotypes that is based on a thorough understanding of the physiological factors mediating successful conceptus-uterine interactions during these three critical periods of conceptus loss.

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