Comparative aspects of placental efficiency

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Litter size is often proposed as the trait that could have the greatest impact in improving reproductive efficiency of pigs. Efforts to select directly for increased litter size have generally been unsuccessful and highly variable. As a result, several attempts have been made to identify critical physiological components that control litter size, with the underlying assumption that augmenting these components would improve this important trait. One attempt at improving physiological components has involved the selection of animals for increased uterine capacity, as measured by the number of fetuses or piglets that a female can carry successfully to term. Recent evidence indicates that one critical component of the uterine capacity in pigs is placental efficiency, or the body weight of a piglet divided by the mass of its placenta. It is easy to determine the average placental efficiency in a litter, but variation among conceptuses within a litter for this trait can be substantial, leading to the conclusion that placental efficiency is an individual conceptus trait. It is suggested that the limited success of selection for an increased uterine capacity results, at least in part, from a misguided view that 'uterine capacity' is strictly a maternal trait. Uterine capacity is better defined as the mass of placental tissue that a pregnant female can support to term, and involves phenotypic variation in both the dam and her offspring. This definition of uterine capacity allows maximization of both uterine size and placental efficiency in future attempts to increase litter size in pigs.

Introduction

A critical element limiting reproductive efficiency in pigs is the large number of potential conceptuses that are lost during gestation (Dziuk, 1987; Lawrence, 1993; Pope, 1994; Rohrer *et al.*, 1999). A number of studies over the last 85 years have highlighted the impact of conceptus loss, particularly from day 12 to day 18 of gestation, on litter size (Hammond, 1914; Corner, 1923; Perry, 1954; Hanly, 1961; Perry and Rowlands, 1962; Scofield, 1972; Dziuk, 1987; Pope, 1994). In general, there is agreement that between 30 and 40% of the embryos formed are lost during this peri-elongation–attachment period (reviewed by Pope, 1994). Recent evidence indicates that embryo losses after day 18 of gestation are significant

and that variation in placental function may contribute to these losses (Wilson *et al.*, 1998, 1999a, 2000). Late embryonic and early fetal losses are particularly critical in commercial crossbred sows in which the ovulation rate is very high (approximately 26 oocytes; Wilson *et al.*, 2000). Therefore, although 30–40% of the embryos are lost between day 12 and day 18 of gestation, the number of conceptuses present at day 25 of gestation is much greater than the number of embryos that survive to term (Foxcroft, 1997; Wilson *et al.*, 2000). In this review, recent work to elucidate the role of the conceptus in determining individual placental size and function, the role of modulation of the uterine environment in altering placental size and function, and the mechanism by which variation in placental size may influence the number of conceptuses that survive beyond days 20–25 of gestation, is described.

Ford (1997) presented the results of nearly a decade of research comparing the prolific Meishan pig to its distant relatives, the commercial occidental breeds. The overwhelming conclusion was that the Meishan pig embryo shows a reduced growth rate during early gestation compared with that of the other breed (Youngs *et al.*, 1993, 1994; Rivera *et al.*, 1996; Ford, 1997; Wilson and Ford, 1997) and concomitantly shows a markedly smaller and more vascular placenta in late gestation (Ford, 1997; Biensen *et al.*, 1998; Wilson *et al.*, 1998). Litter size was greater in Meishan gilts as compared with Yorkshire pigs (one of the occidental breeds used for comparison) despite similar uterine size and ovulation rate (Bazer *et al.*, 1988; Christenson, 1993; Galvin *et al.*, 1993; Lee *et al.*, 1995; Ford, 1997; Biensen *et al.*, 1998; Wilson *et al.*, 1998). Biensen *et al.* (1998) suggested that, in addition to the known impacts of ovulation rate or uterine size, variation in conceptus–uterine interaction must also limit conceptus survival and litter size. When both Yorkshire and Meishan embryos were co-transferred into a common uterine environment (either Meishan or Yorkshire gilts), fetal and piglet body weights at or near term were similar for the littermate Meishan and Yorkshire fetuses and piglets, despite the fact that Meishan conceptuses developed on smaller placentae (approximately 70% of the mass of the placentae of their Yorkshire littermates regardless of an overall breed-of-dam effect; Wilson *et al.*, 1998, 1999b). This critical observation indicates that the difference observed in placental size between straight bred Meishan and Yorkshire conceptuses is not simply a result of an overall smaller conceptus, but of an apparent dissociation of placental and fetal growth (Biensen *et al.*, 1998, 1999; Wilson *et al.*, 1998). As a result of this apparent dissociation, the ratio of fetal or piglet body weight to placental mass (placental efficiency) was used as a measure of placental function (Ford, 1997; Wilson *et al.*, 1999a). At farrowing Meishan conceptuses had placental efficiencies of 8.7 ± 0.4 and 6.3 ± 0.5 when gestated in Meishan and Yorkshire recipient female pigs, respectively. In contrast, Yorkshire conceptuses had placental efficiencies of 4.1 ± 0.9 and 3.4 ± 0.8 when gestated in Meishan and Yorkshire female pigs, respectively (Ford, 1997).

Pattern of placental growth and function

In general, placental growth, as measured by mass, increases exponentially between day 20 and day 60 of gestation (Pomeroy, 1960; Knight *et al.*, 1977). The growth of the placenta then plateaus from day 60 to day 110 of gestation, and this is followed by a secondary increase immediately before term (Pomeroy, 1960; Knight *et al.*, 1977; Biensen *et al.*, 1998; Wilson *et al.*, 1998). This pattern of growth emphasizes what has been observed in occidental breeds. This placental growth pattern was observed in Yorkshire pigs, but Meishan pigs have a smaller placenta throughout gestation and do not show a preterm increase in placental mass (Ford, 1997; Biensen *et al.*, 1998; Wilson *et al.*, 1998). Several workers have reported that placental mass does not change after day 70 of gestation; however, these authors all ceased measurement of placental mass on or before day 105 of gestation, the time of the initiation of

the secondary increase (Knight *et al.*, 1977; Vallet *et al.*, 1996; Klemcke and Christenson, 1997). Data presented by Knight *et al.* (1977) indicate an evident increase (approximately 25%) in placental mass between day 90 and day 100 of gestation. This increase is obscured by a relatively uncharacteristic peak in placental mass in animals killed on day 70 of gestation (Pomeroy, 1960; Biensen *et al.*, 1998). In the study by Knight *et al.* (1997), a second set of animals was unilaterally hysterectomized–ovariectomized to establish a limiting uterine environment or capacity (Knight *et al.*, 1977). In these unilaterally hysterectomized–ovariectomized animals, a peak in placental mass was not observed at day 70 of gestation. However, there was a similar (approximately 25%) increase in placental mass between day 90 and day 100 of gestation; this difference was greater than the difference in placental mass between the intact and unilaterally hysterectomized–ovariectomized animals on day 80 of gestation (Knight *et al.*, 1977).

The surface area of the chorioallantoic membrane increases rapidly from day 35 to day 70 (Knight *et al.*, 1977). On day 35, the surface area is approximately 250 cm^2, whereas at day 70 it is approximately 1000 cm^2 (Knight *et al.*, 1977; Biensen *et al.*, 1998). By days 60–70 of gestation, there is an interlocking network of fetal and maternal microvilli, increasing the massive exchange surface of the placenta (Friess *et al.*, 1980; Björkman and Dantzer, 1987; Biensen *et al.*, 1998). From day 70 to day 100 of gestation, there is little change in the surface area of the placenta (Knight *et al.*, 1977). However, at some time after day 100 there is a marked increase in the surface area of the placenta, reaching approximately 1500 cm^2 (Biensen *et al.*, 1998), or doubling in size by day 110 of gestation (Wigmore and Strickland, 1985). The surface area for exchange is increased greatly by microscopic folding compared with that described by simply spreading out the intact chorioallantoic membrane (Björkman and Dantzer, 1987; Dantzer and Leiser, 1994; Biensen *et al.*, 1998).

The area for contact between the chorionic ectoderm and the luminal epithelium by the folding of the chorionic membrane into the permanent folds of the endometrium is increased markedly by the development of microscopic interdigitations, referred to as primary rugae, along the feto–maternal interface at about day 35 to day 40 of gestation (Friess *et al.*, 1980; Björkman and Dantzer, 1987; Leiser and Dantzer, 1988; Dantzer and Leiser, 1994). During the final third of gestation, the functional surface area for nutrient and waste exchange is increased further by the development of an additional tier of interdigitation along the primary rugae, referred to as secondary rugae (Friess *et al.*, 1980; Björkman and Dantzer, 1987). These microvilli are between 0.8 and 1.0 μm in length, and 0.08 μm in diameter, and occur at approximately 85 per μm^2 (Björkman, 1965).

An important component in the function of the placenta during gestation is the development of a sufficient absorptive area, not only in the physical size of the placenta, but also in the number and density of blood vessels for nutrient exchange (Friess *et al.*, 1980; Leiser and Dantzer, 1988; Reynolds and Redmer, 1995; Biensen *et al.*, 1998). By day 70 of gestation, the placental vasculature accounts for approximately 3.7% of the total volume of the chorioallantoic membrane (Biensen *et al.*, 1998). The density of blood vessels remains relatively constant during late gestation and occupies 3% of chorioallantoic membrane volume by day 90, and 2.5% of chorioallantoic membrane volume by day 110 of gestation (Biensen *et al.*, 1998). Furthermore, Wilson *et al.* (1998) reported that in farrowed placentae, the vascular volume was approximately 4% of placental volume. Pigs are described as having all six potential tissue layers present between the maternal and fetal blood supplies (that is, epitheliochorial as classified by Grosser, 1933). However, the maternal and fetal capillaries for exchange can migrate towards each other, reducing the thickness of the respective epithelial layers such that the distance between endothelial cell membranes is approximately 2 μm (Friess *et al.*, 1980, 1982).

The primary role of the placenta is to provide for fetal nutrition, gas exchange and waste removal throughout gestation (Dantzer, 1982; Munro, 1986). There are four main pathways whereby solutes can pass from maternal blood to fetal blood (Sibley *et al.*, 1997). The first pathway is simple flow-limited diffusion. Molecules such as oxygen and carbon dioxide readily cross cell membranes and, therefore, their transfer from maternal to fetal circulation is limited only by the rate of delivery to the site of transfer (Björkman, 1973; Leiser and Dantzer, 1988; Sibley and Boyd, 1992). The second pathway is protein-mediated transport. The diverse transporter proteins involved can be active transporters or passive transporters, symporters or antiporters, or ion channels (Sibley *et al.*, 1997). Finally, there are two types of transport of which the activity in the placenta is poorly understood: paracellular and endocytosis–exocytosis (Dantzer, 1982; Friess *et al.*, 1982; Sibley *et al.*, 1997). Paracellular transfer involves transfer through the extracellular fluid surrounding the cells of the placenta. Endocytosis–exocytosis involves engulfing solutes into an endocytotic vesicle, vesicular transport through the cell and exocytotic expulsion at the opposite pole. Endocytosis–exocytosis has been observed in pigs in structures referred to as transfer tubules (Sperhake, 1971 (in Friess *et al.*, 1980); Friess *et al.*, 1980, 1982; Dantzer, 1982). Simple flow-limited diffusion is regulated not only by the rate of maternal and fetal blood flows, but also by the arrangement of the endometrial and placental vasculature with respect to each other (Carter, 1989; Carter and Myatt, 1995). These arrangements are generally described by how closely they reflect particular fluid mechanical models, and include concurrent, crosscurrent and countercurrent exchange (Carter, 1989). Of these, concurrent exchange is least efficient (50% theoretical maximal transfer), countercurrent exchange is most efficient (100% theoretical maximal transfer) and efficiency of crosscurrent exchange is between these two values (Carter, 1989). In pigs, placental transfer of freely diffusible nutrients appears to rely on a vascular anatomy that is either concurrent or possibly crosscurrent (Friess *et al.*, 1982; Leiser and Dantzer, 1988). Transporter protein-mediated transfer relies on the density and relative activity of the transporters, and is generally not limited by the rate of blood flow. In pigs, protein-mediated transfer appears to be concentrated in the troughs of the chorionic folds (adjacent to the ridges of endometrial folds; Friess *et al.*, 1980, 1982; Poston, 1997; Sibley *et al.*, 1997). Transported solutes include, but are not limited to, glucose, amino acids and ions, such as sodium, potassium, calcium and protons (Davies, 1960; Battaglia, 1986; Faber and Thornburg, 1986; Lester, 1986; Sibley *et al.*, 1997). In addition to transfer across the interface between the uterine luminal epithelium and chorionic epithelium, large macromolecules (for example, uteroferrin) produced in the endometrial glands are absorbed intact by the placental areolae (Perry, 1981; Friess *et al.*, 1982; Roberts *et al.*, 1986; Leiser and Dantzer, 1994).

By using the gross measurement of placental efficiency as an indicator of overall placental function (for example, diffusion, active transport, umbilical and uterine blood flow, surface area and areolae number), total function has been emphasized over component function. However, the component that may be most important, and into which further investigation has been initiated (see below), is the density of blood vessels in the chorioallantoic membrane (and associated endometrium). Placental efficiency is very low (0.06–0.15) from day 30 to day 40 of gestation (Spies *et al.*, 1959; Knight *et al.*, 1977; Wilson *et al.*, 2000; Fig. 1), but begins to increase very rapidly by day 50 (that is, approximately threefold; 0.6) and continues to increase, although at a reduced rate, until term (Knight *et al.*, 1974, 1977; Dalton and Knight, 1983; Wilson *et al.*, 2000; Fig. 1). This pattern of increased placental efficiency is critical to the exponential growth of the fetal component of the conceptus with regard to limited growth of the placenta after day 70 of gestation. It would appear that there is a second inflection point in the placental efficiency curve as the animal nears term (Fig. 1). It is suggested that the increase in placental efficiency is attenuated by the secondary increase in placental mass from
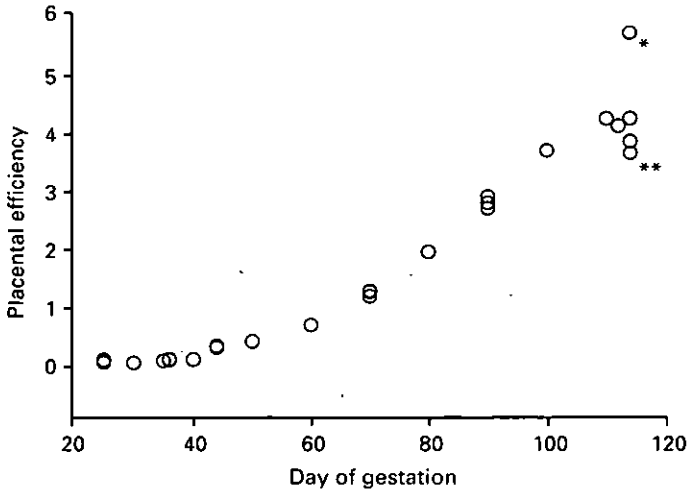
Fig. 1. Pattern of placental efficiency (fetal weight : placental mass) throughout gestation in pigs. Data summarized from several sources (Spies *et al.*, 1959; Knight *et al.*, 1974, 1977; Dalton and Knight, 1983; Ford, 1997; Wilson *et al.*, 1998, 1999a, 2000). *Individuals born to female pigs selected for greater than average placental efficiency. **Individuals born to female pigs selected for lower than average placental efficiency.

day 100 to day 110 of gestation to term. These data support the contention that the pig may be reaching a maximization of placental function coinciding with the end of gestation, which would probably be critical to the rapidity with which fetuses become nutritionally distressed in cases of delayed parturition.

Variation in placental size and function

The hallmark of placental efficiency is the marked variation that is present within a litter. This variation was characterized in an experiment using straight bred Yorkshire litters in which the umbilical cords of individual piglets were tagged at birth to allow piglets to be matched with their placentae. In eight litters, placental efficiency was 4.2 ± 0.2, which is very similar to that observed by Ford (1997) and Wilson *et al.* (1999a). However, the placental efficiency of individual conceptuses in all eight litters ranged from 2.7 to 7:4 (Wilson *et al.*, 1999a), and in one litter from 3.8 to 7.4. In this initial study, and in several subsequent studies, variation in placental efficiency was not associated with variation in the body weight of the fetus (prenatally) or piglet (natally), but was negatively associated with variation in the mass of the placenta (Biensen *et al.*, 1999; Wilson *et al.*, 1999a, 2000). This finding was observed not only near term when fetal growth is at a maximum and probably close to the limit for placental function, but was also evident as early as day 25 of gestation (Wilson *et al.*, 2000). Indeed, during the critical period between day 25 and day 45 of gestation when uterine capacity becomes limiting (that is, crowding reduces conceptus survival; Dziuk, 1968; Dhindsa and Dziuk, 1968; Fenton *et al.*, 1972; Pope *et al.*, 1972; Knight *et al.*, 1977; Huang *et al.*, 1987; Wilson *et al.*, 2000), there is a negative association between placental mass and placental efficiency (Wilson *et al.*, 2000). Furthermore, as uterine capacity becomes limiting, the number of viable conceptuses in a litter is no longer associated with ovulation rate and begins

to be associated with the average placental efficiency for that litter (Wilson et al., 2000). As expected, as placental mass reached a plateau at about day 60 of gestation, and the fetus continued to grow, placental efficiency was > 1 between day 60 and 70 of gestation (Fig. 1). Factors that result in variation in placental size have been investigated. Direct effects, generally via application of steroids during gestation, were examined by Spies et al. (1959), Knight et al. (1974), McGovern et al. (1981) and Wilson and Ford (2000). Indirect effects were observed by causing uterine crowding using superovulation, superinduction or unilateral hysterectomy–ovariectomy (Dhindsa and Dziuk, 1968; Dziuk, 1968; Fenton et al., 1972; Pope et al., 1972; Knight et al., 1977; Huang et al., 1987). Unfortunately, as variation in placental function per se was not the objective of these studies, only average placental efficiencies could be derived for treatment groups and the degree of variation within each litter was not evident. Treatment of sows with oestrogen, progestogen or a combination of both on different days of gestation can stimulate placental growth (Spies et al., 1959; Knight et al., 1974; McGovern et al., 1981; Wilson and Ford, 2000) and crowding can limit placental growth (Knight et al., 1974, 1977). However, neither steroid treatment nor uterine crowding appears to have much effect on placental efficiency during gestation (Spies et al., 1959; Knight et al., 1974, 1977; Dalton and Knight, 1983). It is suggested that placental efficiency is a unique trait of each individual conceptus and that treatments altering placental mass also alter fetal weight as a result of a fairly static functionality of an individual placenta. However, in contrast, in an experiment in which Meishan female pigs were treated with oestradiol on day 12 and day 13, or on day 13 and day 14 of gestation, a 40% increase in placental mass was observed at day 112 of gestation (Wilson and Ford, 2000). In these animals, placental efficiency was reduced compared with that of untreated controls. Whether the ability to alter placental efficiency markedly in Meishan female pigs is a result of a breed difference or is related to the lack of a secondary increase in placental mass after day 100 of gestation has not been established.

As pigs have a diffuse epitheliochorial type of placentation, its function is thought of as blood flow-limited, meaning that nutrient and gas fluxes across the maternal placental interface are limited by the rates of uterine and umbilical blood flows. Placentae of Meishan pigs do not increase in size from mid- to late gestation, but in contrast to placentae of Yorkshire pigs, undergo a marked increase in the proliferation of blood vessels in the chorioallantoic membrane that is in close contact with the associated endometrial vasculature (Biensen et al., 1998; Wilson et al., 1998). The marked increase in the density of placental blood vessels may increase the rate of nutrient and waste product exchange per unit area of placental–endometrial interface (Biensen et al., 1998). Divergence in the strategy used to acquire the nutrients required by the developing fetus is most notable after day 70 of gestation when the fetus has grown to a size at which it begins to exert significant metabolic demands on the placenta (Biensen et al., 1998; Wilson et al., 1998). Between day 70 and day 110 of gestation, vascular density of the Meishan placenta increases twofold, whereas Yorkshire placental surface area increases by approximately 50%; however, significant littermate variation was observed in both breeds (Biensen et al., 1998).

The potential role of placental-derived angiogenic factors in modulating placental efficiency has been investigated by Vonnahme et al. (2001). Vascular endothelial growth factor (VEGF) is a potent angiogenic and vascular permeability factor that is produced by the epithelium of both the placenta and endometrium during gestation in pigs (Winther et al., 1999; Vonnahme et al., 2001; Vonnahme and Ford, 2001). Expression of VEGF mRNA is relatively low during early gestation (that is, days 25–45). At some time after day 45 of gestation (mid-way through the initial period of rapid placental growth), expression of VEGF mRNA continues to increase until term (Vonnahme et al., 2001). The potential significance of

placental production of VEGF is evident by a positive correlation throughout gestation between the relative amount of mRNA being produced by a placenta and the density of blood vessels in the placenta (Vonnahme *et al.*, 2001). Furthermore, there was a positive association between the relative amount of VEGF mRNA present in a placenta and the efficiency of that placenta (Vonnahme *et al.*, 2001).

Impact of placental efficiency on uterine capacity

Several authors over the past 30 years have indicated that if the number of conceptuses surviving beyond day 18 of gestation is increased, the 'capacity' of the uterus will begin to have a negative impact on litter size at approximately day 30 of gestation (Fenton *et al.*, 1972; Pope *et al.*, 1972; Huang *et al.*, 1987; Wilson *et al.*, 2000). Development of the early conceptus was characterized in a commercial line of pigs that had a very high ovulation rate (> 26 oocytes), in which 40% of potential conceptuses were lost by day 25 (Wilson *et al.*, 2000). Between day 25 and day 35 of gestation there was an additional loss of approximately four conceptuses on average, supporting the role of the uterus in limiting litter size, even in a case in which no experimental manipulation was needed to increase the number of potential conceptuses. Conventionally, this limitation has been viewed simply as the absolute number of conceptuses that can be supported to a defined point of gestation, most notably parturition (Fenton *et al.*, 1972; Pope *et al.*, 1972; Chistenson *et al.*, 1987; Huang *et al.*, 1987). This view of uterine capacity has been instrumental in the advancement of our understanding of components important for limiting litter size (Christenson *et al.*, 1987; Vallet *et al.*, 1996; Rohrer *et al.*, 1999; Pearson *et al.*, 2000). However, in light of recent data, a revision of the terminology used is important (Wilson *et al.*, 1999a; Vallet *et al.*, 2001). In particular, uterine capacity should be defined more correctly as the total amount of placental mass a pregnant female pig can support to term. Therefore, it will include both an endometrial surface area for contact component and a component related to the average efficiency of the placentae in that litter (Wilson *et al.*, 1999a; Wilson and Ford, 2000). The uterine component of uterine capacity may not be adequately described strictly by a measure of surface area, but variation may occur in endometrial function per unit area. If so, a greater understanding of how to measure endometrial or uterine function and how it varies may allow for an even better understanding of how 'uterine capacity' is regulated and how it limits litter size.

Heritability of placental efficiency

Reproductive characteristics traditionally show a very low heritability. Indeed, it has been suggested by some authors that the critical nature of reproduction has resulted in the presence of a large number of genes that show few alleles and, therefore, have a low potential for selection. This modified view of uterine capacity was used to select male and female pigs of normal birth weight from within a herd that showed either greater than average or lower than average placental efficiency (Wilson *et al.*, 1999a). When gilts selected for high placental efficiency that had been mated to boars selected for high placental efficiency farrowed, the placental masses of their piglets were 40% lower than those farrowed by low placental efficiency gilts mated to low placental efficiency boars (Fig. 1). The resultant realized heritability was 0.37 (Wilson *et al.*, 1999a). More importantly, sows with high placental efficiency farrowed more than three live pigs per litter than did sows with low placental efficiency (12.8 ± 0.7 versus 9.5 ± 0.6, respectively). Furthermore, similar decreases in placental mass and increases in litter size were observed for sows with high placental efficiency than in sows with low placental efficiency when mated to the same boars and allowed to farrow a second

time (Wilson *et al.*, 1999a). Vonnahme and Ford (2001) established that placentae of conceptuses resulting from mating boars and gilts selected for high placental efficiency have a greater placental expression of VEGF mRNA in addition to a greater placental efficiency, than conceptuses resulting from mating boars and gilts selected for low placental efficiency, with unselected controls being intermediate. Vallet *et al.* (2001) used gilts that were unilaterally hysterectomized–ovariectomized from lines selected for ovulation rate, uterine capacity or unselected controls and failed to find an increase in placental efficiency in those selected for uterine capacity (simply measured as number of conceputses) compared with controls. Vallet *et al.* (2001) observed an increase in placental efficiency in the line selected for ovulation rate. More importantly, in the 422 litters that were collected across all three lines, the heritability of placental efficiency was noteworthy for a reproductive trait (0.29 ± 0.08; Vallet *et al.*, 2001), particularly when compared with reported heritabilities for uterine capacity and litter size (0.09, Young *et al.*, 1996; and 0.16, Hertzer *et al.*, 1940, respectively).

Conclusion

A greater understanding of the physiological basis of traits such as litter size will probably result in more successful attempts to improve the character of interest through either alterations in management or genetic selection. The realization that gestation is an active and integrative process is key to furthering this understanding. Inherent variation as well as the apparent lack of plasticity in the relative efficiency of placental function in pigs is a critical component of uterine capacity. Such variation may explain why selection simply for the number of conceptuses present in a crowded uterus without regard to variation in placental efficiency has not been successful. In addition, an important concept of placental efficiency in pigs is the consistent lack of association with fetal or piglet weight and consistent negative association with placental mass. These associations indicate that either large or small fetuses or piglets can develop on small or large placentae, but that in general large placentae are relatively less efficient than smaller placentae. As we continue to develop and refine understanding of the reproductive biology of the pig, variation in the developmental regulation and final function of the placenta should provide an insight into conceptus loss after day 30 of gestation, as well as the size, number and potentially the uniformity of piglets at birth.

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