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Embryonic and fetal development in different genotypes in pigs

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It is widely accepted that uterine capacity, not ovulation rate, is the greatest restraint on litter size in pigs. Recently, the reproductive strategy(s) of the Chinese Meishan pig, a breed which farrows three to five more piglets per litter than US or European pig breeds, has come under intense scrutiny. It was initially determined that the Meishan female could farrow more viable piglets per litter than US or European pig breeds, with a uterine size and ovulation rate equivalent to those of less prolific breeds. It has become apparent that the Meishan conceptus exhibits a reduced trophectoderm mitotic rate during the preimplantation period, elongates from fewer cells and remains smaller throughout gestation compared with conceptuses from less prolific US or European pig breeds. This strategy by the Meishan conceptus for a lower growth rate results in a marked reduction in conceptus loss through day 18 of gestation compared with less prolific breeds. An additional strategy is required in the Meishan to allow the larger number of viable fetuses to survive after day 30 of gestation when uterine capacity becomes limiting. Our research has demonstrated that the rapid growth of the fetus in US pig breeds appears to require continued placental growth to increase the surface area for nutrient exchange. In contrast, the increased numbers of smaller Meishan fetuses achieve the same increase in placental efficiency by markedly increasing the density of placental blood vessels at the fetal–maternal interface. This proliferation of placental blood vessels obviates the need for marked increases in placental size.

Introduction

Evidence has rapidly accumulated suggesting that from the time a conceptus enters the uterus, it is subject to modulations of growth, differentiation or both processes through its exposure to a bewildering array of uterine environmental factors (Paria and Dey, 1990; Pollard, 1990; Simmen and Simmen, 1991; Simmen *et al.*, 1995). Furthermore, far from being passive in this process, all evidence points to the fact that both the conceptus and the uterus actively contribute to placental and fetal growth and development throughout gestation in a variety of mammalian species (Venge, 1950; Hunter, 1958; Ferrell, 1991a,b; Youngs *et al.*, 1994).

In this review, I will emphasize the two periods during gestation in the pig that I consider are the most important in determining the number of viable piglets at farrowing. These periods include the peri-implantation period (i.e. days 12–18), and the period from midgestation to term. It is during the peri-implantation period that the greatest numbers of viable conceptuses in a litter are lost (about 75% of the total loss; reviewed by Ford and Youngs, 1993). Fetal weight increases most markedly during the latter half of gestation in pigs, as in other mammalian species, in association with very limited placental growth (Warwick, 1928; Reynolds and Redmer, 1995). Furthermore, on the basis of a number of studies, increased blood flow at the fetal–maternal interface appears to be a primary determinant of increased transplacental exchange during this period of late gestation in livestock species (Ford, 1995; Reynolds and Redmer, 1995). Reynolds *et al.* (1985) demonstrated that in pigs as the number of fetuses in a uterine horn increased (range from two to eight fetuses), the blood flow allotted to each during late gestation progressively declined. Furthermore, as uterine blood flow per

Table 1. Comparisons between breeds in ovulation status and early conceptus development 48–54 h after the onset of oestrus

Parameter	Meishan (n = 66)	Yorkshire (n = 55)
Ovulation status (% of gilts)		
All follicles ovulated	89.4%	92.7%
Some but not all follicles ovulated	7.6%	5.5%
No follicles ovulated	3.0%	1.8%
Conceptus development		
Minimum number of cells[a]	1.5±0.9	1.9±0.3
Maximum number of cells[b]	3.4±0.4	3.3±0.4
Range of cell numbers across all conceptuses	1–8	1–8

[a]Average cell number of the least developed conceptus in a litter.
[b]Average cell number of the most developed conceptus in a litter.
n = number of litters.

fetus declined with increasing numbers of fetuses, umbilical blood flow to these fetuses also declined ($r = 0.70$; $P < 0.01$). The decrease in placental surface area of each conceptus with increasing numbers of fetuses per horn (Knight *et al.*, 1977) may reduce the size of each placental vascular bed, with concomitant reductions in fetal growth.

However, these periods are by no means independent, since the number of conceptuses surviving the peri-implantation period will dictate the uterine space that can be allotted to each for the remainder of gestation. Thus, it is assumed that prolific pig breeds such as the Chinese Meishan, which exhibits a markedly reduced preimplantation conceptus loss when compared with commercial US and European pig breeds (Galvin *et al.*, 1993; Haley and Lee, 1993), must have a strategy for successfully maintaining these larger litters to term. This is difficult to explain as the size of the uterus in Meishan and US and European pig breeds is similar when adjusted for the slaughter weight of the female (Bazer *et al.*, 1988; Lee *et al.*, 1995).

For the past 20 years, the litter size of commercial pig breeds in the US has been relatively constant, despite repeated attempts to define selection criteria for an increased number of piglets (Pork Facts, 1993). This failure to change litter size significantly was the major impetus for the importation of the prolific Meishan pig into the US from China in 1989. The Meishan is known to farrow three to five more viable piglets per litter than US or European pig breeds (Jin *et al.*, 1992). This review will emphasize the most recent information obtained by our group and others from studies in Meishan pigs and provide insight into its prolificacy.

The Peri-implantation Period

An essential period for the establishment of pregnancy in the pig occurs between day 12 and day 18 after mating. During this period, conceptuses expand to 8–10 mm spheres, space themselves uniformly throughout the uterus (Dhindsa *et al.*, 1967; Dziuk, 1968, 1985), elongate to long filamentous forms (Geisert *et al.*, 1982a), and attach to the uterine wall through interdigitation of trophoblastic and endometrial microvilli (Dantzer, 1985).

Coincident with expansion and elongation, the day 11–12 conceptuses acquire the ability to synthesize oestradiol (Gadsby *et al.*, 1980; Pusateri *et al.*, 1990). Oestradiol is measurable in large spherical blastocysts, and then increases rapidly during tubular expansion into filamentous forms, before declining precipitously after elongation (Pusateri *et al.*, 1990). On days 11–12 after mating, the progesterone-primed endometrium is very sensitive to conceptus oestradiol, which will alter stromal and epithelial development (Geisert *et al.*, 1991) and secretory activity (Geisert *et al.*, 1982b; Morgan *et al.*, 1987). During the late preimplantation period, blastocysts are especially dependent

Table 2. Comparisons between breeds of ovulation rate, conceptus recovery on days 11 to 12 of gestation and litter size

Parameter	Meishan	(*n*)	Yorkshire	(*n*)
Ovulation rate[a]	16.5±0.5	(70)	16.3±0.4	(93)
Number of conceptuses collected[a]	12.5±0.5	(69)	12.3±0.5	(82)
Litter size[b]	12.3±0.4	(42)	8.9±0.4	(66)

[a]Means ± SEM are not different between breeds, $P > 0.30$.
[b]Calculated from another group of gilts of similar reproductive age. Means ± SEM are significantly different, $P < 0.01$.
n = number of litters.

upon endometrial secretion of specific hormones, growth factors and nutrients for normal growth and development (Roberts and Bazer, 1988). Owing to the marked variation among littermates in conceptus size at this time of gestation, the most advanced conceptuses in the litter begin the synthesis of oestradiol before other conceptuses (Stroband and Van der Lende, 1990). The increase in uterine luminal oestradiol results in increased uterine blood flow and vascular permeability, and alters the amount and composition of endometrial secretions to provide a suitable micro-environment for the increasingly complex requirements of the conceptus (Flint, 1981; Ford *et al.*, 1982; Van der Meulen *et al.*, 1989; Stroband and Van der Lende, 1990). The less well-developed conceptuses in the litter are thus exposed to this rapidly changing uterine environment, resulting in their eventual demise (Dziuk, 1987; Pope *et al.*, 1990; Pope, 1994).

The high incidence of preimplantation conceptus loss in US and European pig breeds was first noted by Hammond (1914), and has since been confirmed to average approximately 30% (Dziuk, 1987). The period surrounding implantation is considered especially critical for conceptus survival, and most loss occurs between days 12 and 18 after mating (Scofield, 1972).

Uterine capacity has been defined as the maximum number of fetuses that can be successfully carried to term when the number of potentially viable conceptuses is not limiting (Christenson *et al.*, 1987). Treatments imposed to exceed uterine capacity in pigs (for example superovulation, superinduction) will produce large numbers of viable conceptuses, but only to approximately day 30 of gestation (Dziuk, 1968; Pope *et al.*, 1972). Thereafter, the effect(s) of the limiting uterine capacity is evident, in that these females will give birth to numbers of piglets equivalent to those found in untreated pigs.

Meishan versus Yorkshire conceptuses during the preimplantation period

If a large number of Meishan and Yorkshire gilts in our herds were compared at the same reproductive age (i.e. two to five post-pubertal oestrous cycles), no obvious differences among breeds were observed in the interval from the initiation of oestrus to ovulation or the conceptus stages recovered on day 2 (Table 1). Furthermore, ovulation rate and the number of viable conceptuses recovered on day 12 are almost identical, even though these Meishan gilts farrow approximately three more piglets than do the Yorkshire gilts (Table 2). We have used Meishan and Yorkshire gilts of these equivalent reproductive ages for our studies on the control of litter size. This is critical, since ovulation rate increases progressively to reach 30 to 40 ova shed in older multiparous Meishan sows, while remaining at 14 to 16 in US and European pig breeds (Christenson, 1993).

In our herds, Meishan and Yorkshire conceptuses elongate synchronously on days 11–12 after mating (Fig. 1), a time similar to that reported for other US and European pig breeds (Youngs *et al.*, 1994). A similar range of conceptus development occurs in both breeds throughout this period (Fig. 1). The apparent greater absolute diversity within the Yorkshire litters is accounted for by a similar within-litter variation (standard deviation) in litters with an increased mean conceptus diameter. However, if the within-litter coefficient of variation, which takes into consideration the difference in

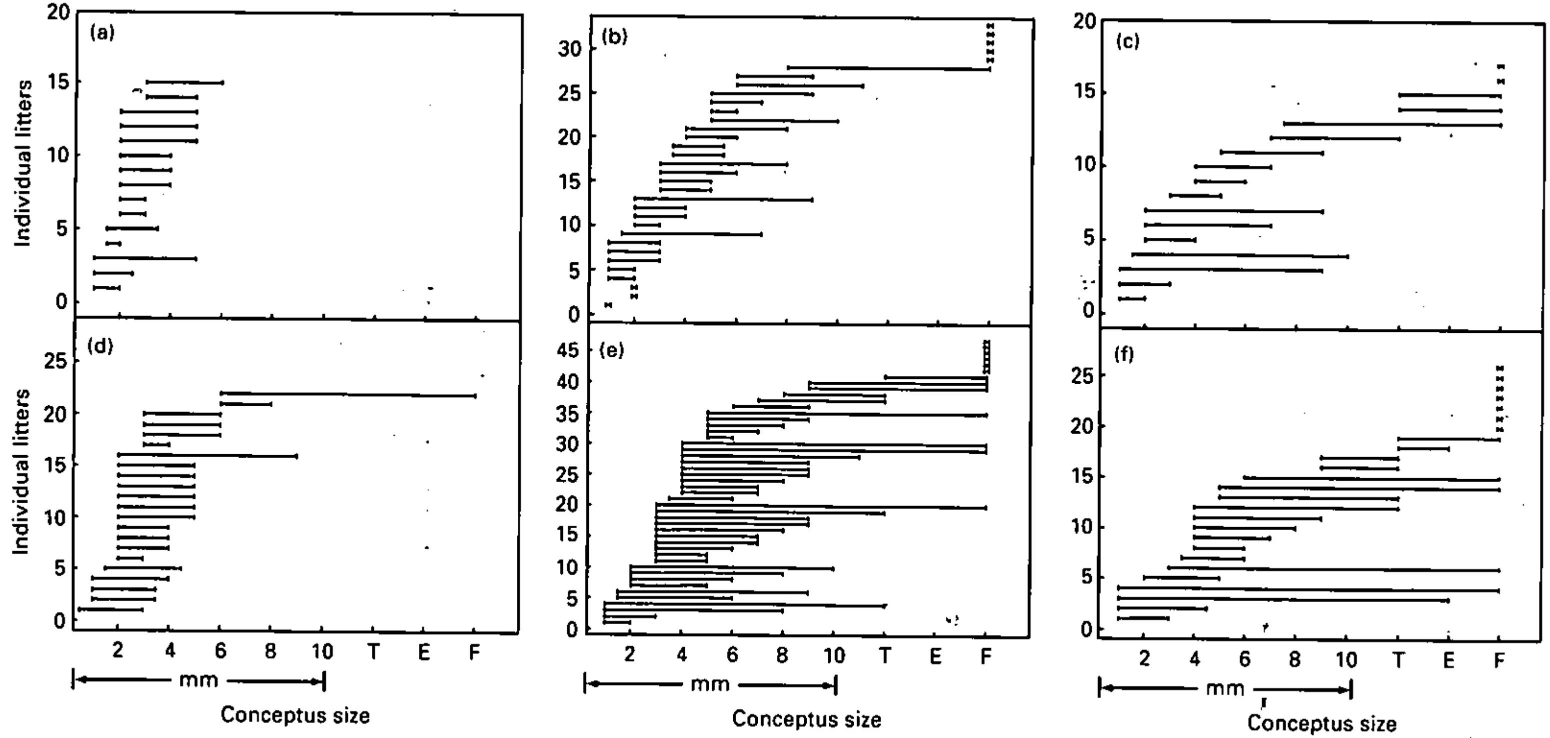

Fig. 1. Range of conceptus development of individual Meishan (a, b, c) and Yorkshire (d, e, f) female pigs from days 11 (a, d), 11.5 (b, e) and 12 (c, f) of gestation (first day of oestrus and mating = day 0). T, tubular; E, elongating; F, filamentous.

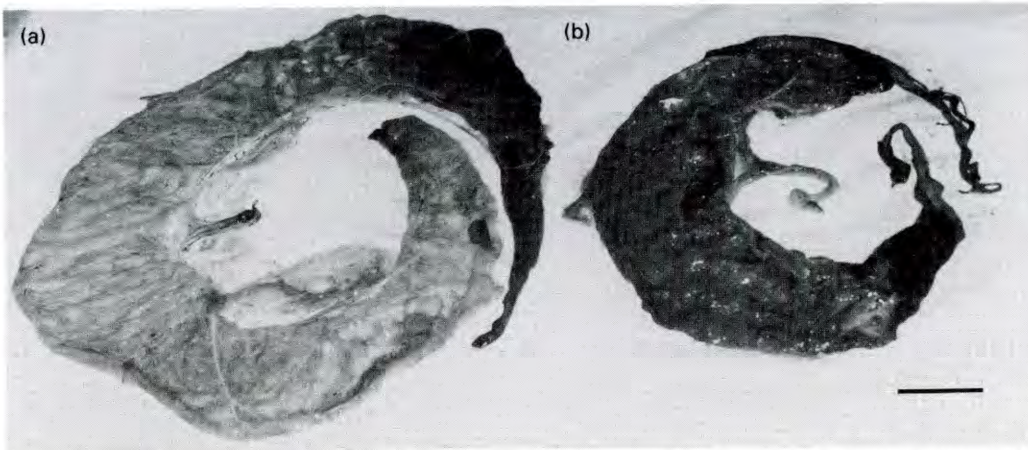

Fig. 2. A large relatively avascular Yorkshire placenta (a) and a small highly vascular Meishan placenta (b) recovered from a single Yorkshire recipient female pig. These placentae were matched to fetuses of very similar birth weight. Scale bar represents 10 cm.

mean conceptus diameter, is calculated, there are breed differences (i.e. differences in Yorkshire litters are greater than Meishan litters). Thus, although the average within-litter diversity is relatively constant across breeds, the absolute diversity in a litter is associated with the degree of conceptus development in that litter. These data are consistent with the published reports that Meishan conceptuses at days 11–12 are smaller when they initiate steroidogenesis (Wilson and Ford, 1997) and elongate (Youngs *et al.*, 1994) than Yorkshire conceptuses. Furthermore, Wilson *et al.* (1995) reported that Meishan filamentous conceptuses were shorter and contained fewer cells than Yorkshire conceptuses on day 14.

The smaller size of the Meishan versus the Yorkshire preimplantation conceptus results from its markedly small numbers of trophectoderm (TE) cells from day 5 (Rivera *et al.*, 1996) to day 12 (Wilson and Ford, 1997) in similar stage conceptuses. Furthermore, the reduction in numbers of TE cells in Meishan versus Yorkshire conceptuses has been shown to result from a lower mitotic rate of these cells in the Meishan conceptus (Wilson and Ford, 1997). Conley *et al.* (1992) have shown that P450 17α-hydroxylase/17–20 lyase is the enzyme most closely associated with pig conceptus oestradiol production, and have localized this enzyme exclusively in the TE (Conley *et al.*, 1994). In association with its reduced population of TE cells on days 11–12, Meishan conceptuses produce and secrete less oestradiol into uterine luminal fluid than do similar stage Yorkshire conceptuses (Wilson and Ford, 1997). Furthermore, these researchers demonstrated that the decreased oestradiol concentrations in uterine luminal fluid of Meishan versus Yorkshire females is associated ($r = 0.57$; $P < 0.001$) with a lower concentration of insulin-like growth factor-I (IGF-I) in the same flushings.

The potential interrelationship between uterine luminal oestradiol and IGF-I may be crucial for the further rapid growth and development of the conceptus as it prepares to undergo elongation. Evidence supporting this hypothesis includes: (1) the presence of receptors for IGF-I on the preimplantation pig conceptus (Corps *et al.*, 1990), (2) the finding that insulin, a hormone known to bind the IGF-I receptor, increases protein synthesis by, and the growth of, the preimplantation pig conceptus (Lewis *et al.*, 1992) and (3) the expression of steroidogenic enzymes important for oestradiol biosynthesis has been correlated with the concentration of IGF-I in uterine luminal fluid (Ko *et al.*, 1994). These and other findings have led Simmen *et al.* (1995) to propose a feed forward mechanism in which the oestradiol produced by the rapidly expanding pig blastocyst stimulates endometrial IGF-I production which, in turn, stimulates conceptus steroidogenic enzymes and further oestradiol synthesis. However, this story is far from complete, as Chastant *et al.* (1994) failed to detect IGF-I receptors on pig conceptuses from day 4 to day 10 of gestation, or on TE cells from the placenta on day 20. These data suggest that the reduced size and oestradiol secretory activity of the

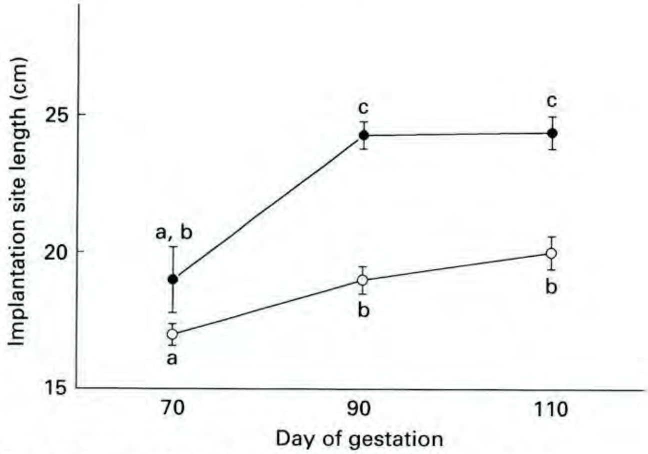

Fig. 3. Average length of the uterine horn occupied by each conceptus on days 70, 90 and 110 of gestation in (○) Meishan and (●) Yorkshire female pigs. [a,b,c] Means ± SEM with different superscripts are significantly different ($P < 0.01$).

Meishan conceptus, when compared with Yorkshire conceptuses throughout blastocyst expansion and elongation, may allow for greater conceptus survival and potential litter size.

Finally, a reciprocal conceptus transfer experiment between Meishan and Yorkshire females was conducted to evaluate the specific influences of uterine environment versus conceptus genotype on preimplantation conceptus growth rate (Youngs *et al.*, 1994). In this study, conceptuses were transferred from Meishan or Yorkshire donors to synchronous recipients of either breed on day 2 and removed on day 12 of gestation. Meishan conceptuses were always smaller than Yorkshire conceptuses at a similar stage on day 12, regardless of uterine environment, but conceptuses of both breeds contained fewer cells and were smaller when recovered from a Meishan uterus than when recovered from a Yorkshire uterus. Furthermore, conceptuses of both genotypes produced markedly less oestradiol when contained in a Meishan uterus than when contained in a Yorkshire uterus. These data suggest that both uterine environmental and conceptus genotype affect preimplantation conceptus growth, and that only uterine environmental differences affect oestradiol secretion. These data are consistent with the concept that the uterine environment (Meishan versus Yorkshire) is the sole determinant of conceptus oestradiol secretory activity.

Latter Half of Gestation

In pigs, it is generally accepted that placentae that are smaller than average size limit fetal growth (Knight *et al.*, 1977). As the demands of the fetus for nutrients and oxygen increase markedly in late gestation, placental insufficiency should become most evident during this time. The pig placenta is diffuse according to the classification of Grosser (1909) and of the epitheliochorial type. Over the mouths of the uterine glands the allantochorionic membrane is not attached to the endometrial epithelium, but forms regular or irregular areolae which first appear on day 30 of gestation (Brambell, 1933). The interareolar placenta is composed of chorionic ridges and their corresponding endometrial folds. Placental efficiency is determined by its surface area of contact with the uterine wall (chorionic villus surface area) and the thickness of the placental membranes. Baur (1977) has shown that the chorionic villus surface area increases progressively throughout gestation in pigs, but lags behind fetal weight. However, there is clear histological evidence of a progressive thinning of the effective placental barrier separating the fetal and maternal bloodstream in pigs (Friess *et al.*, 1980). This thinning, which accelerates during the last third of gestation, results from a marked

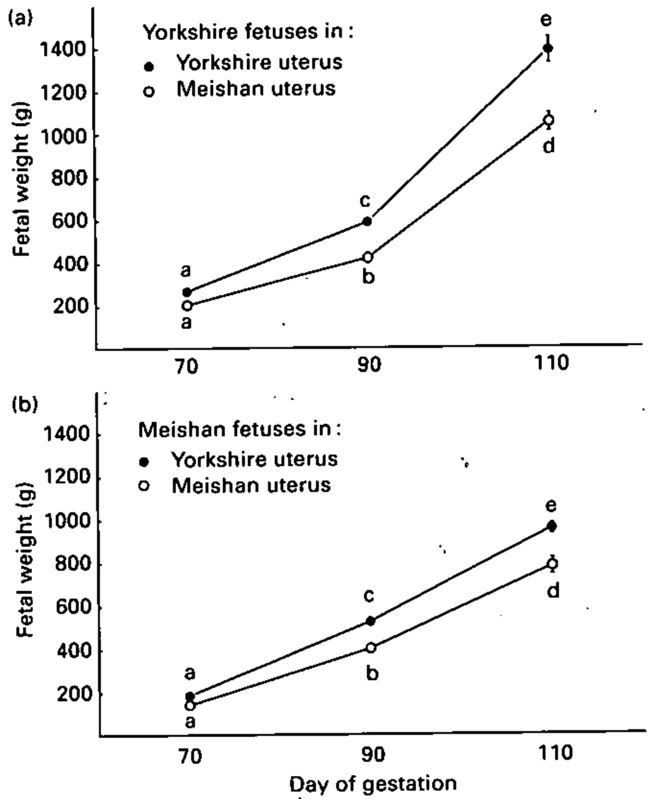

Fig. 4. Weight of (a) Yorkshire and (b) Meishan fetuses in Yorkshire and Meishan uteri on days 70, 90 and 110 of gestation. [a,b,c,d,e] Within a fetal breed, means ± SEM with different superscripts are significantly different ($P < 0.05$).

indentation of fetal vessels into the trophoblast, and the indentation of maternal capillaries into the uterine epithelial cells at the fetal–maternal interface. At the end of pregnancy, the distance between fetal and maternal capillaries is often less than 2 μm.

Meishan versus Yorkshire conceptuses during late gestation

We next investigated the consequences of the observed differences in uterine environment and conceptus genotype on subsequent placental and fetal growth between Meishan and Yorkshire pigs. Rivera *et al.* (1994) transferred 20 conceptuses (ten Meishan plus ten Yorkshire) into the oviducts of synchronous Meishan or Yorkshire recipient females on day 2 after oestrus, and recovered the conceptuses on day 90 of gestation. More ($P < 0.05$) fetuses were recovered from Meishan recipients on day 90 than from Yorkshire recipients (14.8±0.4 versus 10.0±1.9 fetuses, respectively). Placental weight was markedly reduced for conceptuses recovered from Meishan versus Yorkshire recipient females, whereas fetal weight was affected both by recipient breed and by fetal genotype. Meishan and Yorkshire fetuses gestated in Meishan uteri to day 90 were similar in weight, averaging 381±23 g, but were markedly smaller than either Meishan (498±20 g) or Yorkshire (613±16 g) fetuses gestated in Yorkshire uteri. Interestingly, day 90 Yorkshire fetuses were larger than Meishan fetuses when both were gestated in Yorkshire recipient females. These data suggest that the Meishan uterine environment restricts placental growth of both Meishan and Yorkshire conceptuses, ultimately limiting fetal growth by day 90 of gestation. It also appeared that the larger placental sizes of

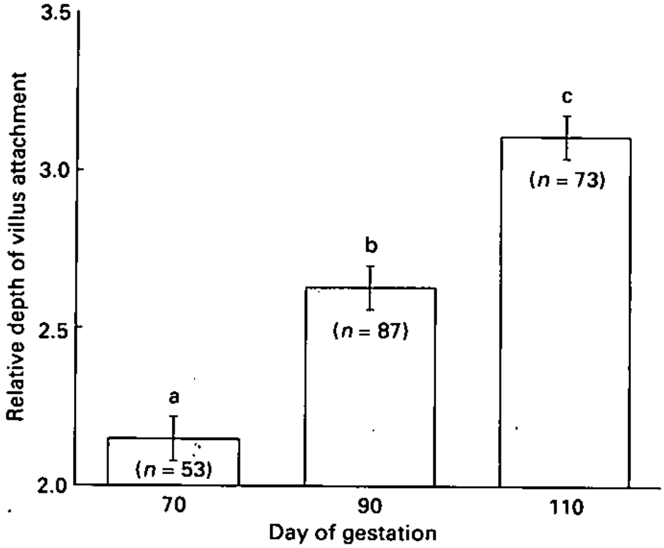

Fig. 5. The relative depth of villus attachment of placentae of Meishan versus Yorkshire pigs on days 70, 90 and 110 of gestation. [a,b,c]Means ± SEM with different superscripts are significantly different ($P < 0.05$).

Meishan and Yorkshire conceptuses in Yorkshire uteri allowed the expression of breed-specific differences in fetal growth.

Owing to this breed-specific (Meishan versus Yorkshire) difference in fetal weight of littermates gestated in Yorkshire recipients, a subsequent experiment was conducted with Yorkshire recipients only. As previously described, both Meishan ($n = 10$) and Yorkshire ($n = 10$) conceptuses were transferred to Yorkshire recipients on day 2, but instead of recovering conceptuses on day 90, the females were allowed to farrow. At farrowing, each piglet was caught as it appeared at the vaginal opening and the exposed umbilical cord was tagged to match the piglet's number, cut and allowed to retract. In this way, each piglet could be matched with the appropriate placenta at expulsion. Unexpectedly, two visually distinct placental types were observed during the farrowing of each recipient Yorkshire female. Relatively large and blanched placentae were exclusively matched to Yorkshire fetuses, while smaller, very reddened (i.e. more vascular) placentae were matched to Meishan fetuses. Two placentae expelled from a single Yorkshire recipient female and matched to a Yorkshire and a Meishan piglet of equal weight are shown in Fig. 2. In these mixed litters of Meishan and Yorkshire fetuses, the piglet weight (g): placental weight (g) ratio was calculated as an estimate of placental efficiency for each conceptus. The piglet weight: placental weight ratio differed markedly ($P < 0.05$) for Meishan conceptuses, which averaged 8.7±0.4 when compared with littermate Yorkshire conceptuses which averaged 3.4±0.8. Interestingly, these breed differences in fetal weight: placental weight ratios are due predominately to differences in placental weight (approximately 66%) rather than to any marked differences in piglet weight (7%).

Meishan and Yorkshire recipient females carrying either Meishan or Yorkshire fetuses were slaughtered on days 70, 90 and 110 of gestation to characterize more fully the specific differences in placental and fetal growth and development between the Meishan and Yorkshire breeds. At slaughter, the length of each uterine horn was determined and fetal measurements were taken (weight and crown–rump length) and a section of each individual placenta and attached endometrium was collected for histological evaluation of the following: (1) number of villi per unit length of placenta (villar number), (2) length of villus attachment per unit length of placenta (villar depth), and (3) percentage of placenta occupied by blood vessels (placental vascular density). Each placenta was then weighed and its length determined as well as the length of its implantation site in

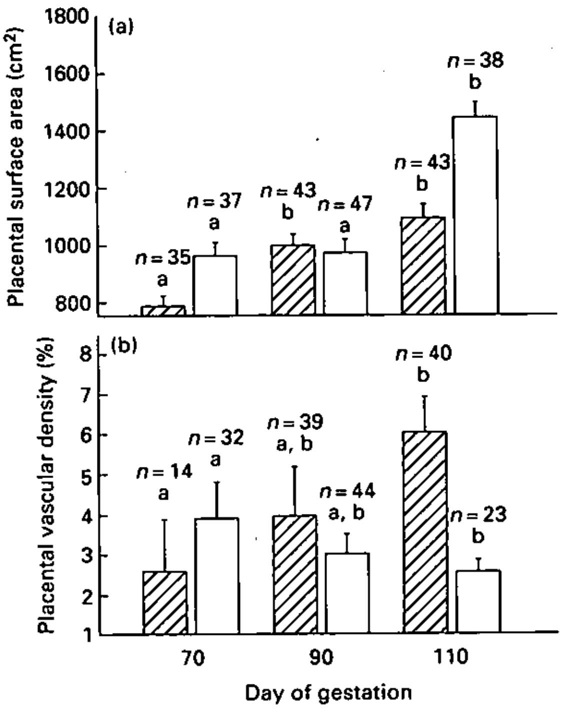

Fig. 6. Surface area (a) and associated blood vessel density (b) of placentae of Meishan (▨) and (□) Yorkshire pigs on days 70, 90 and 110 of gestation. [a,b]Within a breed type, means ± SEM with different superscripts are significantly different ($P < 0.05$).

the uterus. In addition, each placenta was cut along the anti-mesometrial border so that it could be spread out on a flat surface and traced with a planimeter to determine its surface area.

There was no effect of uterine position in which a conceptus resided (i.e. tip, middle or base) or the number of conceptuses in a horn on any fetal or placental measurement. In addition, no effect of breed or day was observed on total uterine length; however, conceptuses in Meishan uteri occupied a smaller ($P < 0.01$) length of uterine horn than conceptuses in Yorkshire uteri (Fig. 3). Furthermore, implantation site length of conceptuses in both Meishan and Yorkshire uteri increased by about 20% from day 70 to day 110 of gestation. The decreased implantation site length of conceptuses in Meishan versus Yorkshire uteri is reflected by the fact that both Yorkshire and Meishan fetuses grew more slowly in a Meishan than in a Yorkshire uterus from day 70 to day 110 (Fig. 4a,b). The number of chorionic villi per unit length of placenta was similar for Meishan and Yorkshire placentae. Thus, the length of villus attachment per unit length placental–endometrial interface reflects the relative depth to which chorionic villi extended into the endometrial folds (Fig. 5). As depicted, villi length increased progressively from day 70 to day 110 of gestation and was similar across uterine and fetal breeds.

However, the pattern of placental growth differed markedly between Meishan and Yorkshire conceptuses. Surface area of Yorkshire placentae remained relatively constant from day 70 to day 90, before increasing ($P < 0.001$) markedly by day 110 (Fig. 6a), while exhibiting a progressive decline in placental vascular density (Fig. 6b). In contrast, the surface area of Meishan placentae increased only moderately from day 70 to day 90, and failed to exhibit any further increase from day 90 to day 110 (Fig. 6a). Throughout this period, and in contrast to the Yorkshire placenta, the Meishan placenta showed a marked increase ($P < 0.01$) in vascular density (Fig. 6b). The fetal weight : placental weight ratio of these conceptuses on day 110 was markedly higher ($P < 0.01$) for Meishan than for Yorkshire conceptuses gestated in Meishan (6.07±0.35 and 4.65±0.20) or Yorkshire (5.08±0.17 and 4.35±0.15) uteri, due predominantly to differences in placental size.

Conclusion

The numbers of blood vessels per unit placental area at the uterine interface will determine in large part the capacity for nutrient exchange between the fetus and dam. As a result of this progressively increasing efficiency of nutrient and oxygen extraction per unit area of placenta, the Meishan conceptus can support the growth and development of a viable fetus with a much smaller placenta than is found in US pig breeds. Since the real limitation to litter size is the available space in the uterus, conceptuses that occupy less uterine space would result in larger litters.

The Meishan pig, therefore, has two separate yet complimentary strategies for increasing litter size. Firstly, the Meishan conceptus develops from fewer cells in the early stages of development than do similar stage conceptuses of US or European pig breeds, resulting in reduced oestradiol production. This reduced oestradiol production by the preimplantation Meishan conceptus results in less marked changes in the composition of uterine histotroph, allowing more conceptuses to survive beyond day 18 of gestation than for US or European pig breeds. Secondly, the Meishan conceptus develops a smaller, more vascular placenta than that found in US or European pig breeds. Furthermore, owing to their smaller size, more Meishan conceptuses are accommodated by the uterus after day 30 of gestation, when uterine size becomes limiting. Therefore, each Meishan placenta requires less endometrial space for nutrient exchange throughout late pregnancy when fetal demands are increasing, leading to the potential for larger litters.

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