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Intrauterine position and adjacent fetal sex affects fetal and placental growth throughout gestation, but not embryonic viability, in pigs selected for component traits of litter size☆

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ABSTRACT

Intrauterine position and sex of adjacent fetuses in litter bearing species have been implicated in physiological and behavioral differences of offspring. The effects of uterine position and sex status of flanking fetuses with crowded uterine conditions on fetal and placental growth rate was tested. Gilts were unilaterally hysterectomized-ovariectomized at 160 d of age and mated at approximately 280 d of age, with fetal harvest at 45, 65, 85, or 105 d of gestation. Uterine position relative to the cervix, fetal status (alive, dead, sex), fetal weight, and placental weight were recorded at harvest. Each fetus was coded as adjacent to 0, 1, or 2 opposite sex fetuses and analyzed using an ANOVA fitting contemporary group, line, and flanking fetal sex code as fixed effects with sire as a random effect. The fraction of live fetuses in each classification (0, 1, 2) was 26.4%, 50.1%, and 23.4%, respectively, indicating no effect on fetal survival. Fetal weight was affected by flanking sex status between 65 d ($P < 0.05$) and 105 d ($P < 0.001$), with means at 105 d of 800.0 ± 20.3, 748.5 ± 17.8, and 672.7 ± 25.2 g, respectively for flanking sex status codes 0, 1, 2. Placental weight was similarly affected ($P < 0.01$) by flanking sex code, but only at 105 d. It is concluded that fetal growth and placental development in pigs is influenced by sex status of adjacent fetuses. This could be a potential source of variation in behavioral and reproductive differences later in life.

1. Introduction

Prenatal programming in pigs alters development of fetal growth with lasting consequences for adult phenotype (Foxcroft et al., 2009). Limitations in uterine space causes increased embryonic loss and fetal intrauterine growth retardation leading to greater

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within-litter variation in piglet weight at birth with lesser average birth weights of litters, which can reduce preweaning survival (Lay et al., 2002) and decrease postnatal growth performance (Tilley et al., 2007). Uterine capacity is a component trait of litter size that can be used in genetic selection (Bennett and Leymaster, 1989; Gama and Johnson, 1993). Selection for uterine capacity in swine for 11 generations resulted in an estimated 1.6 more live pigs of similar birth weight at term compared to an unselected control line (Freking et al., 2007). Uterine capacity, therefore, is generally considered an important component of prenatal programming in pigs (Foxcroft et al., 2006).

Intrauterine position and sex of the neighboring fetuses have a wide range of effects on fetal growth, morphology, and later behavioral characteristics of mice (vom Saal and Bronson, 1978, 1980b; vom Saal, 1981). There are similar effects of a lesser extent in swine (Wise and Christenson, 1992; Tarraf and Knight, 1995). Males surrounded by two males *in utero* had increased aggressiveness and postnatal growth rate (Rohde Parfet et al., 1990b) and females had altered sexual receptivity and duration of estrus (Rohde Parfet et al., 1990a). The probability of a female fetus being positioned between two male fetuses increases as the proportion of males in the litter increases (male sex ratio). Age at first pubertal estrus was at a younger age and first service conception rates was less in gilts from litters with greater male sex ratios (Lamberson et al., 1988; Drickamer et al., 1997). How these effects might be related to uterine capacity is unknown. The purpose of this study was to determine if the effects of intrauterine position and sex of adjacent fetuses in a crowded uterine environment are similar to that reported for normal litters, and whether differences in component traits of litter size affect the response.

2. Materials and methods

All animal procedures were reviewed and approved by the U.S. Meat Animal Research Center (USMARC). Data are from three of four replicates of a prior study comparing fetal growth throughout gestation in lines of pigs selected for ovulation rate or uterine capacity with a randomly selected control line. As fetal sex was not recorded at day 25 of gestational age, this subset was not considered a part of the current study. Details regarding genetic background and development of selection lines can be found in the previous report (Freking et al., 2007). Briefly, unilateral hysterectomy-ovariectomy (UHO) surgery was performed at approximately 160 d of age. Gilts were subsequently observed for signs of estrus and naturally mated at approximately 280 d of age to individual boars within the same selection line, avoiding paternal half-sib matings. Mated gilts in four contemporary groups were assigned to be sacrificed at 45, 65, 85, or 105 d of gestation (± 2 d) while distributing paternal half-sibs across as many of the time points as possible. Gilts were harvested at the USMARC abattoir and reproductive tracts were immediately recovered. The cervix and broad ligament were closely trimmed and each tract opened along the antimesometrial border. Each fetus was removed by detachment from the umbilical cord. Intrauterine position, fetal sex, and status (alive, dead, mummy) was recorded. Observation of a heartbeat was required for live status to be recorded. Weight of each fetus was recorded and placental tissue matching each fetus was separated from the endometrium and weighed.

Data from 297 litters were evaluated. Data were coded to evaluate possible effects when each fetus was adjacent to zero, one, or two fetuses of the opposite sex. To interpret growth curves and survival data the initial complete data set was edited by removal of the data for fetuses in the first and last positions in the uterine horns to remove bias. This data editing occurred because for the fetuses in the end positions there was no possibility of these being flanked on both sides by a fetus of either sex. After this editing, data for a total of 343, 651, and 303 fetuses were included in the analyses for when there were no, one, or two opposite sex flanking fetuses, respectively. The proportion of surviving fetuses in each flanking fetal sex code was evaluated by Chi-square analysis. Fetal and placental weight were analyzed using mixed-model ANOVA procedures fitting contemporary group, line, and flanking fetal sex code as fixed effects and sire as a random effect. A nonlinear function was fitted to the data of fetal weight to establish unique growth curves for each flanking sex code. Parameter estimates were derived using the Gauss-Newton method. Parameters A, B, and k were estimated for each flanking fetal sex code and also for data pooled across these codes to describe the function:

$$f_{(\mathrm{d})} = \mathrm{A}e^{(\mathrm{B}-\mathrm{kd})\mathrm{d}} \quad (1)$$

where $f_{(\mathrm{d})}$ = the weight of the live fetus at a specific day (d) of gestation. Parameter estimates include an intercept A and two terms to describe the instantaneous growth rate B that changes by value k each day of gestation. An *F*-ratio was calculated to test whether the estimation of the parameters specific to each flanking fetal sex code significantly improved the fit of the data relative to estimation of the parameters from the pooled data. The *F*-statistic was calculated as:

$$F = [(\mathrm{RSS_P} - \Sigma\ \mathrm{RSS_{SC}}) / (\mathrm{Rdf_P} - \Sigma\ \mathrm{Rdf_{SC}})] / (\Sigma\ \mathrm{RSS_{SC}} / \Sigma\ \mathrm{Rdf_{SC}})$$

where RSS is the residual sums of squares, Rdf is the residual degrees of freedom, and the subscripts P and SC represent the pooled and contributing flanking fetal sex code specific models, respectively. The comparison of a single equation pooling all three flanking fetal sex codes relative to three sex code-specific equations had 6 df in the numerator. A large *F*-statistic provides evidence that the pooled single model is inappropriate and that fetal growth differs between flanking fetal sex codes.

3. Results

The UHO procedure was used to generate data representing litter size as a function of uterine capacity expressed by each gilt. The number of live fetuses ranged from 2 to 13. Fetal and placental weights at each uterine position were expressed as a deviation from the mean weight of the litter. These data indicate that fetal and placental weights were greater ($P < 0.0001$) at the cervical and

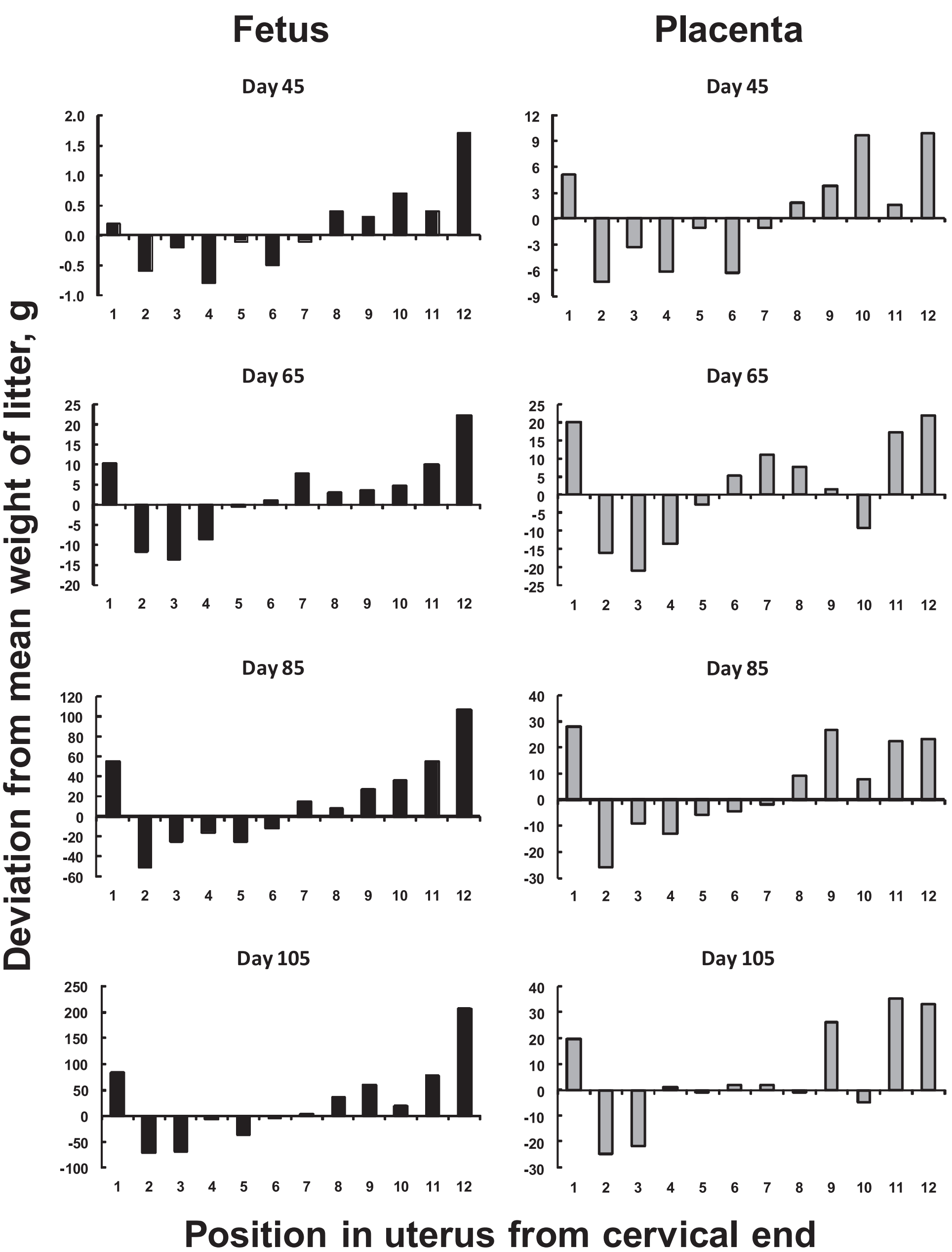

Fig. 1. Fetal and placental weight, expressed as a deviation from the mean weight of the litter, in relation to fetal position within the uterine horn at day 45, 65, 85, and 105 of gestation with crowded uterine conditions; Fetuses and placentas were numbered consecutively from the tubal to cervical end of the horn of gilts that had undergone unilateral hysterectomy-ovariectomy before mating.

tubal ends of the uterine horn (Fig. 1). By day 105 of gestation, fetuses in the 2nd and 3rd position from the cervical end of the uterus were most negatively affected. The percentage of dead fetuses at 45, 65, 85, and 105 d of gestation were 15.8%, 11.2%, 16.7%, and 14.1% respectively. The relative ranking between lines for the number of live fetuses remained unchanged after day 45. Only fetuses that could be flanked by two other fetuses were considered for Chi-square analysis. The frequency of live fetuses classified as being surrounded *in utero* by 0, 1, or 2 fetuses of the opposite sex did not differ from expected values of 25%, 50%, and 25% for each classification (Table 1), and was no affect ($P > 0.10$) of line.

The combined effects of sex of adjacent fetuses did not affect placenta weight at day 45 ($P = 0.89$), 65 ($P = 0.39$), and day 85 ($P = 0.20$) of gestation; however, at day 105 of gestation, fetuses surrounded by two fetuses of the opposite sex had placentas that weighed less ($P < 0.01$) then fetuses surrounded by two fetuses of the same sex (Fig. 2). There was no effect of adjacent fetal sex on fetal weight at day 45 of gestation ($P = 0.59$). Weight of fetuses surrounded by two fetuses of the opposite sex was less at day 65 ($P < 0.05$), 85 ($P < 0.01$), and 105 ($P < 0.001$) of gestation than that of fetuses surrounded by two fetuses of the same sex

Table 1
Frequency of live fetuses classified as being surrounded *in utero* by no, 1, or 2 fetuses of the opposite sex.

No of flanking fetuses of opposite sex	Frequency	
	Number	Percent (%)
0	343	26.4
1	651	50.1
2	304	23.4

Data combined for male and female fetuses from day 45, 65, 85, and 105 of gestation; Data for first and last fetus from each litter removed to eliminate end bias.

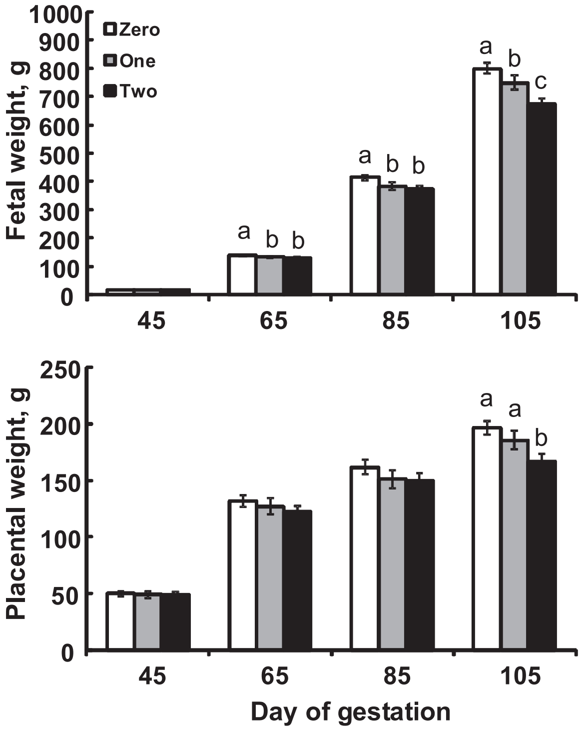

Fig. 2. Least-squares means for fetal weight and placental weight of fetuses surrounded by no, one, or two fetuses of the opposite sex with crowded uterine conditions at 45, 65, 85, and 105 d of gestation; There was an effect of sex of the surrounding fetuses on fetal weight at day 65 ($P < 0.05$), 85 ($P < 0.01$), and 105 ($P < 0.001$) of gestation and for placental weight at day 105 ($P < 0.01$) of gestation.

(Fig. 2). Parameters were estimated to describe fetal growth as a function of gestational age (Table 2). A general exponential form of fetal growth was evaluated using Eq. [1] as previously described (Freking et al., 2007). The null hypothesis that a single pooled function more effectively described the data than functions specific for each flanking fetal sex code was rejected ($P < 0.005$).

Table 2
Estimate of parameters describing fetal growth as a nonlinear function of gestational age.

Flank code[b]	Parameter estimates[a] ± SE			Residual		
	A	B	k	Sum of squares	df	*F*-ratio[c]
0	0.125 ± 0.101	0.147 ± 0.078	0.0006 ± 0.0001	9921836	592	12.3[*]
1	0.155 ± 0.111	0.140 ± 0.016	0.0006 ± 0.0001	13830087	874	
2	0.176 ± 0.197	0.137 ± 0.025	0.0006 ± 0.0001	3826304	300	
Pooled	0.153 ± 0.075	0.141 ± 0.011	0.0006 ± 0.0001	28726446	1772	

[a] $f(d) = Ae^{(B-kd)d}$, where A, B, and k represent curve parameters estimated using the Gauss-Newton method and d represents days of gestation.
[b] Pooled equation includes fetuses surrounded by no, one, and two fetuses of the opposite sex.
[c] *F*-ratio tests the hypothesis that the flank code-specific functions are equivalent; A large *F*-value indicates that a common function is inappropriate and that fetal growth differs between individual flank-codes; Numerator df are 6 for the pooled equation.
* $P < 0.005$.

4. Discussion

The data from the present study indicate that with crowded uterine environments, the effects of intrauterine position on fetal and placental development throughout gestation occur earlier than in less crowded intact litters. Contrary to results previously reported, sex of adjacent fetuses does not negatively affect fetal survival, even when uterine conditions are crowded. An important finding is that the effects of intrauterine position on fetal and placental development during gestations is not related to genetic differences in ovulation rate and uterine capacity, component traits of litter size in swine.

Fetuses at the end of the uterine horns are larger than fetuses at other uterine positions (Waldorf et al., 1957; Perry and Rowell, 1969; Wise and Christenson, 1992). The observation that fetuses at the cervical and ovarian end of the reproductive tract in UHO-treated gilts strengthens this conclusion to include crowded uterine environments. The greater weight of fetuses at the ends of the reproductive tract may be due to the variation in embryo spacing, uterine space available for development, or differential availability of nutrients. In rodents and rabbits, larger fetuses at the ends of the horn are thought to be a result of increased nutrient exchange owing to a more favorable blood supply than those of fetuses in the middle of the uterine horn; the haemodynamic theory. The arrangement of the uterine arterial supply in these species is described as a loop vessel that is supplied at both ends and extends parallel along the length of the uterine horn with lateral branches at different locations in the uterine horn (see McLaren, 1965). In contrast, the uterine artery of the pig is directed towards the middle of the uterine horn and branches in the mesometrium in a radial pattern (Oxenreider et al., 1965), thus, this anatomical blood flow arrangement would not be consistent with the haemodynamic theory. Furthermore, with the larger fetuses at the cervical and ovarian end of the uterine horn there were no differences in vascular supply (Perry and Rowell, 1969). In another study, conceptuses at the ovarian and cervical ends of the uterine horns were crushed on day 35 of pregnancy and development of adjacent fetuses were compared to nonadjacent fetuses at day 105 of gestation (Vallet et al., 2011). Weights of the placenta and fetus adjacent to the crushed conceptus were greater (6% and 10%, respectively) than non-adjacent fetuses. By virtue of location, fetuses at the ends of the tract can be flanked by only one other conceptus. These fetuses, therefore, may have an advantage over those at other positions *in utero* because they are less affected by sex of the adjacent fetuses.

Wise and Christenson (1992) reported that a fetus flanked *in utero* by two fetuses of the opposite sex at 70 and 104 d of gestation in normal litters occurred less frequently than expected. It isn't clear why fetuses positioned between others of the opposite sex would be preferentially lost due to death *in utero*. One reason for this result might be bias due to fetuses at the ends of the reproductive tract. Fetuses at the ends of the reproductive tract of gilts can be flanked by only one fetus. Consequently, fetuses at the ends of the tract would be classified as being flanked by either no or one fetus of the opposite sex, thus creating bias in the frequency of these flanking fetal sex classes. In the current study, there was only consideration of the data when there was the possibility of a fetus being flanked by two live adjacent fetuses, and with this consideration the fraction of live fetuses represented by each classification of flanking fetal sex code (0, 1, 2) occurred at the expected frequencies. It can be concluded, therefore, that being surrounded by fetuses of the opposite sex when uterine space is limited did not affect fetal survival. Results of previous studies with swine indicate that as uterine space becomes limited, the sex ratio of the litter increases in favor of females (Chen and Dziuk, 1993; Tse et al., 2008), and fetuses that died during the last third of gestation were males (Wise and Christenson, 1992). In the present experiment, in which uterine space was limited and the data for fetuses on the ends were censored, the frequency of live male (n = 662) fetuses was not different from the frequency of female (n = 635) fetuses, indicating that limitations in uterine space, even early in gestation, does not lead to a skewing of litter sex ratios.

Rhode Parfet et al. (1990b) reported that birth weight (day 112 of gestation) was not affected by sex status of the adjacent fetuses, but the numbers of observations were small (n = 31 litters). In an experiment with more animals, Wise and Christenson (1992) reported that fetal weight at 104 d of gestation was reduced when fetuses were positioned between others of the opposite sex. The results in this previous study are consistent with results from the current experiment; however, unlike with the study of Wise and Christenson (1992), where there were no differences in fetal weight at 70 d of gestation, in the present study weight of fetal piglets surrounded by two opposite sex fetuses was less before 70 d of gestation. Effects of adjacent fetal sex on fetal growth are considered to be evident earlier in gestation as a consequence of a crowded uterine environment resulting from UHO treatment (Tarraf and Knight, 1995).

The effect that sex of the surrounding fetuses had on fetal weight was not influenced by line, which indicates that this altered fetal growth is not related to genetic differences in uterine capacity. Finch et al. (2002) concluded that programming of prenatal growth in the pig occurs before day 30 of gestation when uterine capacity is not limiting (Johnson et al., 1999; Freking et al., 2007). The sex of surrounding fetuses may affect placental development during this early stage of pregnancy, which subsequently retards fetal growth. Differences in placental weight due to sex status of surrounding fetuses were observed only at 105 d of gestation in the current experiment. In contrast, Tarraf and Knight (1995) found that in UHO pregnancies at day 40, placental weight of female fetuses surrounded by male fetuses was less than females at other intrauterine positions. Differences in placental weights in Tarraf and Knight (1995) were not evident at 80 or 100 d of gestation, possibly due to limited numbers of observations, which limited statistical power. There were only 28 total UHO pregnancies (seven pregnancies per gestational stage) and the SEM for placental weight at 80 to 100 d of gestation ranged from 18.9 to 48.9 g; whereas in the current study there were 297 total UHO pregnancies (74 to 75 pregnancies per gestational stage) and the SEM for placental weight at 85 to 105 d of gestation ranged from 5.9 to 8.2 g. In the study of Tarraf and Knight (1995), however, placentas of fetuses surrounded by littermates of the same sex produced more estrone at 100 d of gestation than placentas from fetuses surrounded by fetuses of the opposite sex, suggesting that even without a difference in placental weight, placental function could be altered with sex of adjacent fetuses.

In mice and rats, the alterations of fetal growth and variation in adult phenotype associated with intrauterine position result from transfer of sex steroids between fetuses (vom Saal and Bronson, 1980a; vom Saal et al., 1983, 1990). Because of the epitheliochorial structure of the pig placenta, which differs from the hemochorial placenta of rodents, sex of the adjacent fetus does not affect concentrations of sex steroids in either umbilical blood or allantoic fluid in fetuses at different intrauterine positions of normal (Wise and Christenson, 1992) or UHO litters (Tarraf and Knight, 1995) ranging from day 40 to 104 of pregnancy. Sex of adjacent fetuses, however, did result in differences in thymosin β4, a thymic secretory peptide (Wise and Christenson, 1992), but it is unclear how this might be related to placental function. Proteomic or transcriptomic studies may be necessary to elucidate the mechanisms of the effects that intrauterine position has on fetal growth and placental function in pigs; as it appears to be different from that of the intrauterine position phenomenon in rodents.

The consequence that the intrauterine position phenomenon has for variation in adult phenotype in swine remains to be fully answered. Rohde Parfet et al. (1990b) reported that sex of the adjacent fetuses had no effect on postnatal growth rate of gilts or barrows when feed was available *ad libitum*; however, when limit fed, males that developed *in utero* between two male fetuses gained more weight than other males, and this was attributed to greater aggressiveness, thus, greater access to feed. Sex of the adjacent fetuses had no effect on length of the estrous cycle or ovulation rate of gilts, but puberty tended to be earlier in gilts that were surrounded *in utero* by male fetuses and there was a shorter duration of estrus than in gilts that developed *in utero* between two female fetuses (Rohde Parfet et al., 1990a). There was a major limitation of the approach of Rohde Parfet et al. (1990a; 1990b), which involved slaughtering of sows at 112 d of gestation so that intrauterine position relative to sex of the adjacent fetuses was known. The limitation with this approach is that there cannot be sufficient sample sizes to adequately determine differences in traits that are more highly variable or for behaviors with low frequencies.

The probability of a female fetus being positioned between two male (2 M) fetuses is greater as the proportion of males in the litter increases. Thus, sex ratio of the litter has been used in an attempt to address the long-term consequences of intrauterine position on adult phenotype. Lamberson et al. (1988) reported that as the proportion of males in the litter increased, age at puberty of gilts decreased, which would seemingly confirm the age at puberty of 2 M gilts observed by Rohde Parfet et al. (Rohde Parfet et al., 1990a). Gilts that developed *in utero* between two female fetuses might have potentially greater reproductive success because 0 M gilts had greater sexual receptivity (standing reflex) and because the capacity to express a standing reflex at estrus is positively associated with farrowing rates (Cronin et al., 1982; Knauer et al., 2011). This concept is strengthened by the results reported for gilts from male biased litters (> 60% males) with these gilts having a delayed preovulatory LH surge and decreased conception rates (Drickamer et al., 1997; Seyfang et al., 2018). Furthermore, female mice that developed *in utero* between male fetuses had a shorter reproductive life (vom Saal and Moyer, 1985). Results from a preliminary report indicated that sows born in litters with fewer males (< 15%) subsequently gave birth to larger litters than sows born in litters with more than 50% males (Edgerton and Cromwell, 1986). The limited frequency of litters with sex ratios toward the ends of the distribution profile and the restricted numbers of females from those litters that enter production limit the capacity to confirm many of these observations. The expectation is that continued advancement in reproductive technologies, such as deep intrauterine insemination and sexed semen, will enhance the capacity to control sex ratio of litters and for enhancement of understanding how variation in intrauterine position affects adult phenotype and swine production.

In summary, with a crowded uterine environment, fetuses at the ends of the reproductive tract are larger than the average for the litter and this deviation occurs earlier than in less crowded uterine environments. Fetal and placental growth and development are affected by sex status of adjacent fetuses in crowded uterine environments, but there is no effect of sex status of adjacent fetuses on fetal survival when bias for fetal placement on the uterine ends is removed. With the advent of current selection programs for increased litter size in pigs, most commercial litters now are born under what can be considered crowded uterine environments, and there is renewed interest in selecting for improved uterine capacity. In this regard, the current study demonstrates the effect that impact that being located between fetuses of the opposite sex has on fetal growth is independent of component traits for litter size, including uterine capacity. These intrauterine effects are a potential source of variation in behavioral and reproductive differences later in life. Continued improvement in reproductive technologies should facilitate a greater understanding of the biological effect that results from this variation. With the use of these advanced technologies, the expectation is that there will be identification of new biological markers that are useful in selection programs to account for the effects of prenatal environment on gilt productivity. Selection of the larger birth weight gilts from litters with fewer males would be a strategy that might lead to increased productivity of gilts.

Declaration of Competing Interest

Authors declare no conflict of interest.

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