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G. R. Foxcroft,[3] W. T. Dixon, S. Novak, C. T. Putman, S. C. Town, and M. D. A. Vinsky

Swine Reproduction-Development Program, Swine Research & Technology Centre, University of Alberta, Edmonton, AB, T6G 2P5, Canada

ABSTRACT: The main purpose of this review is to discuss associations between within-litter variation in birth weight, and preweaning survival and postnatal growth in the pig, as the basis for suggesting that the developmental competence of pigs born, as well as the size of the litter, need critical consideration. Extremes of intrauterine growth retardation (IUGR) occur within a discrete subset of fetuses, substantially smaller than their littermates and commonly described as runt piglets. The lower preweaning growth of runt pigs cannot be entirely explained based on their lower birth weight, nor do they show full postnatal compensatory growth. Interestingly, this more complex reprogramming of development in runt pigs can already be identified by d 27 to 35 of gestation. Recently, we reported more universal IUGR effects in commercial dam-line sows, as an indirect response to selection for increased litter size. High ovulation rates (>30 ovulations) in a proportion of greater parity sows are associated with increased numbers of conceptuses surviving to d 30 of gestation, resulting in detrimental effects on placental development of uterine crowding in the early postimplantation period. In turn, this limits nutrient availability to the embryo during a critical period of myogenesis. Consequently, although a reduction in the number of conceptuses occurs by d 50, placental development in the surviving fetuses remains compromised, resulting in IUGR and reduced numbers of muscle fibers at d 90 and at birth, in all surviving littermates. These effects of uterine crowding on fetal and postnatal development are analogous to the detrimental effects of nutritional restriction in gestating sows on fetal myogenesis, birth weight, and postnatal growth. The incompatibility between increased numbers of conceptuses surviving to the postimplantation period, in the absence of increased uterine capacity, offers a biological explanation for increased variability in birth weight and postnatal growth performance reported in greater parity sows. We conclude that a strategy of introducing hyperprolific females into the breeding nucleus, as a means of increasing the numbers of pigs born, needs to be critically evaluated in the context of the overall efficiency of pork production.

Key words: fetus, intrauterine growth retardation, postnatal growth, prenatal programming, swine

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INTRODUCTION

In domestic species such as the pig, the number of offspring born is an important economic trait, and the components of litter size (ovulation rate, embryonic survival, and uterine capacity) responsive to genetic selection are well established (Johnson et al., 1985, 1999). However, as selection for ovulation rate has been associated with selection against early embryonic survival, and because birth weight decreased as litter size increased, Johnson et al. (1999) concluded that selection for uterine capacity might be the most productive approach in genetic selection programs. A recent study of associations among within-litter variation in birth weight and preweaning survival and weight gain, also led to the conclusion that selection for increased litter size that results in more low-birth-weight piglets may not be beneficial, unless measures are taken to improve the survival of the low-birth-weight offspring (Milligan et al., 2002). Thus, both the developmental competence of the pigs born, as well as the size of the litter, needs critical consideration.

Existing literature indicates that a considerable amount of the variation in growth performance after

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[3]Corresponding author: george.foxcroft@ualberta.ca

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birth may be largely determined, and essentially preprogrammed, during fetal development in the uterus (see Foxcroft and Town, 2004). Furthermore, it is likely that these preprogrammed limitations in growth performance will only finally express themselves in the late grower and early finisher stages of production. There is also preliminary evidence that differences in fetal development that will likely affect postnatal growth performance can be present without associated effects in birth weight (Town, 2004). From a practical perspective, sorting pigs by weight at the nursery and grower stages will not resolve the variation in growth performance that is still an inherent characteristic of particular pigs or litters. Thus, we face the conundrum that 13 pigs born in a litter may originate from very different numbers of embryos in the uterus around d 30 of gestation. If relatively high intrauterine crowding is present at d 30, this can critically affect subsequent myogenesis. Our objectives will be to focus this review to justify our hypothesis that an inability to compensate for the negative effect of crowding on placental development limits fetal growth later in gestation and preprograms these litters to have poorer postnatal growth performance and muscle quality at slaughter.

UTERINE CAPACITY AS THE ULTIMATE LIMITATION ON LITTER SIZE

The concept of uterine capacity was established using different experimental approaches to study effects of uterine crowding in the pig. These included uterine ligation, oviduct resection, unilateral hysterectomy and ovariectomy (**UHO**), and superovulation and embryo transfer, and led to the conclusion that when the number of embryos exceeded 14, intrauterine crowding was a limiting factor for litter size born (Dziuk, 1968). Bazer et al. (1969a,b) also concluded that increased embryonic loss, associated with a greater number of embryos in the uterus, was due to maternal limitations and not to inherent limitations of the embryo. They suggested that two physiological mechanisms might be involved. Initially, embryo selection might be the result of competition among embryos for some biochemical factor in the uterus necessary for their continued development. However, in later gestation, intrauterine competition for the establishment of adequate surface area for nutrient exchange between fetal and maternal circulations may act to limit litter size.

In the context of variation in development in the uterus, the concept has been advanced that mechanisms promoting competition among embryos in the preimplantation period will act to reduce within-litter variation in development by selectively removing the least developed embryos (van der Lende et al., 1990). Nevertheless, the more recent results of Père et al. (1997) confirm that, even in sows with "normal" ovulation rates, uterine capacity can affect both litter size and the average birth weight of the litter.

WHEN DOES UTERINE CAPACITY AFFECT FETAL SURVIVAL AND DEVELOPMENT?

Fenton et al. (1970) determined that uterine capacity only becomes a limiting factor for fetal survival after d 25 of gestation. Knight et al. (1977) further defined d 30 to 40 of gestation as the critical period when uterine capacity exerts its effects. Subsequent studies in both intact and UHO females support this conclusion (Vallet, 2000). Vallet et al. (2003) suggested that fetal growth rate is less sensitive to intrauterine crowding than placental growth rate and, as in the prolific Meishan female (Ford and Youngs, 1993), within certain limits of uterine capacity an increase in placental efficiency may initially protect the developing fetus from a limitation in placental size. However, in some populations of commercial sows identified in recent studies (Town, 2004), increased placental efficiency did not compensate poor placental development in sows with even relatively modest intrauterine crowding (15 v. 9 embryos surviving to d 30) and classic effects of intrauterine growth retardation (**IUGR**) were present at d 90 of gestation.

In the context of results from earlier studies of within-litter variation in prenatal development (Adams, 1971; Widdowson, 1971; Hegarty and Allen, 1978; Flecknell et al., 1981), Wootton et al. (1983) suggested that the extremes of IUGR or "runting" were identified within a discrete subset of fetuses. Furthermore, based on data from subsequent studies of the association between within-litter differences in prenatal development and postnatal survival and growth, van der Lende and de Jager (1991) concluded that the lower preweaning growth of the runt pigs born could not be entirely explained on the basis of their lower birth weight and suggested that IUGR or runting had a more complex effect on the developmental potential. Interestingly, data from the same laboratory led to the suggestion that the extent of IUGR within a litter was associated with specific patterns of embryonic survival (van der Lende et al., 1990) and the larger the litters were in the uterus the greater the chance that runt fetuses would be present. Furthermore, these data were consistent with the conclusion that within-litter variation in development was already established at the early fetal stage (d 27 to 35) of gestation.

PATTERNS OF PRENATAL LOSS AND DEVELOPMENTAL POTENTIAL

Preimplantation embryonic losses are still considered the largest proportion of prenatal loss in the pig, with some lesser loss in the postimplantation period that will ultimately reflect uterine capacity (as reviewed by Ashworth and Pickard, 1998). In commercial practice, this generalization likely reflects the situation in gilts in which ovulation rates of 10 to 15, associated with some degree of embryonic loss, are the primary factors limiting litter size. Weaned, first-parity sows also tend to fall into this category. Although ovulation rate may

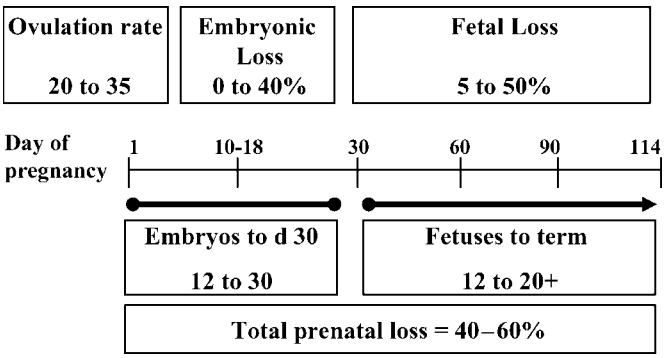

Figure 1. Schematic representation of the changing pattern of prenatal loss observed in multiparous sows in recent studies. Ovulation rate from total number of corpora lutea present at the time of embryonic or fetal dissection.

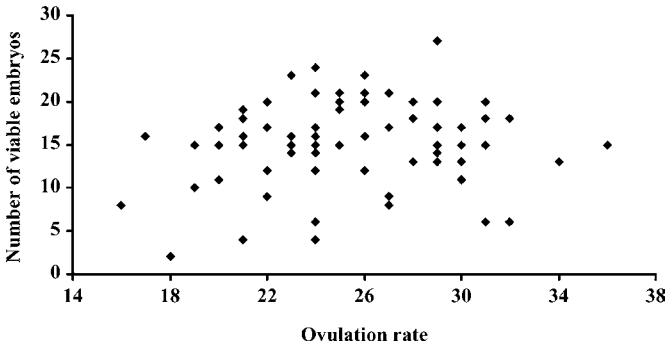

Figure 2. Ovulation rate in relation to the number of viable embryos recovered from the uterus of commercial dam-line sows at d 30 of gestation in the second, third, and fourth parity and greater (Taken from Town et al., 2004a).

be greater (15 to 20 ovulations), many sows tend to be in a catabolic state, which generally decreases embryonic survival to 60 to 65% (Foxcroft, 1997).

However, the dynamics of prenatal loss in existing commercial dam-lines may be changing (Foxcroft, 1997; Figure 1). In these populations, it appears that several generations of direct selection for litter size have indirectly resulted in a discrepancy between the number of conceptuses surviving to the postimplantation period and uterine capacity. Because of markedly increased ovulation rates, associated with good or even modest embryonic survival in the preimplantation period, the number of embryos surviving to the immediate postimplantation period (d 25 to 30) initially greatly exceeds uterine capacity. As a result, a substantial proportion of prenatal loss is now occurring in the postimplantation period in these animals.

Even in individual gilts with 20 or more ovulations, embryonic survival rate can be 100% at d 28 of gestation (Almeida et al., 2000), whereas average first litter size is still only 10 to 12 piglets. In greater parity females, the situation may be even more extreme: mean ovulation rates of 26.6 (Vonnahme et al., 2002) and 24.7 (Town et al., 2004a) have been reported in commercial dam-line sows, with 15 to 20% of greater parity sows having greater than 30 ovulations (Table 1; Figure 2). Despite relatively poor embryonic survival to d 30 (approximately 60% in both studies), numbers of conceptuses in the uterus at d 30 (approximately 15) still exceeded uterine capacity. Consistent with the literature reviewed earlier, uterine capacity then exerted its effects and a significant reduction in the number of conceptuses occurred by d 45 to 50 of gestation. However, as also reported in earlier literature, even this modest increase in uterine crowding around d 30 of gestation had consequences for placental development, seen as a decrease in placental volume (Almeida et al., 2000) and placental weight (Vonnahme et al., 2002; Town et al., 2004a).

Although the size and weight of the embryo was apparently not affected by crowding up to d 44 of gestation, potential impacts on fetal development need careful study. If placental compensatory mechanisms are not adequate, crowding of the uterus in the early postimplantation period may affect fetal development of surviving conceptuses in a manner analogous to IUGR. This raises important questions for both fetal and postnatal development. In the context of commercial grow-

Table 1. Ovulation rate and embryonic survival rate with increasing parity in contemporary gilt and sow populations

Parity	Ovulation rate	Embryo survival to d 30, %	Number of embryos at d 30	Reference
Gilts	17.1 ± 0.6	83.6 ± 4.3	14	Almeida et al. (2000)[1]
1	19.9 ± 1.6	87.5 ± 6.4	17	Zak et al. (1997)[2]
	15.4 ± 2.3	64.4 ± 6.1	10	Zak et al. (1997)[2]
2+	22.1 ± 0.8	69.0 ± 3.3	15	Patterson et al. (1999)[3]
	26.7 ± 0.8	68.0 ± 2.0	18	Vonnahme et al. (2002)[4]

[1]Pig Improvement Company (PIC) F_2 Gilts (n = 22).
[2]PIC F_1 Parity 1 (n = 9).
[3]PIC F_1 Parity 2+ (n = 33); J. Patterson, G. Foxcroft, and F. Aherne, University of Alberta, Canada, unpublished data.
[4]PIC Multiparous (n = 149).

finish performance, a specific interest in effects on the development of fetal muscle fibers, which begin to differentiate around d 35 of gestation in the pig, is particularly important. In contrast to situations in which the occurrence of IUGR is limited to a discrete subpopulation of runt fetuses (Royston et al., 1982; Wootton et al., 1983), we hypothesized that a changing pattern of embryonic loss that results in uterine crowding in early gestation would produce a more uniform effect on placental development that would affect the development of all surviving fetuses (Foxcroft, 1997; Foxcroft and Town, 2004).

FACTORS AFFECTING MUSCLE DEVELOPMENT IN THE PIG

A series of studies in the pig have demonstrated that maternal nutrition during gestation has an effect on piglet birth weight, and that low birth weight is primarily associated with a reduced number of secondary muscle fibers (Handel and Stickland, 1987; Dwyer et al., 1994). Consistent with earlier data of Hegarty and Allen (1978) indicating that runts in the litter have reduced muscle growth potential, Dwyer et al. (1993) established a positive correlation between the total number of muscle fibers and postnatal growth potential, and demonstrated that littermates with a high numbers of fibers grew faster and more efficiently than littermates with a lower number of fibers. Dwyer et al. (1994) further established that the effect of maternal nutrition occurred between d 25 and 50 of gestation, the period immediately preceding secondary muscle fiber hyperplasia.

Effects of maternal nutrition during gestation on fetal development are widely reported, and this area of literature was the subject of an excellent review by Robinson et al. (1999). Furthermore, Maltin et al. (2001) extensively discussed the impact of manipulating myogenesis by various intrauterine manipulations on subsequent muscle development. The early period of myogenesis, involving the differentiation of primary muscle fibers, is generally considered resistant to nutritional manipulation, whereas nutritional effects on differentiation and hyperplasia of secondary fibers have been demonstrated between d 25 and 90 of gestation. However, Rehfeldt and Kuhn (2006) suggest that nutrition may also affect the number of primary fibers differentiating.

From the perspective of using nutritional intervention and other treatments to reduce the variation in birth weight and postnatal growth within litters, it is interesting to note that the greatest reported impact of increased maternal nutrition (Dwyer et al., 1994), treatment with exogenous somatotropin during early gestation (Rehfeldt et al., 2001), and breed of sow (Ashworth and Pickard, 1998), was on the smallest pigs within the litter. These results suggest that relative undernutrition of the smallest fetuses in the uterus is the driver of low birth weight and poor postnatal growth performance. Furthermore, the early data of Widdowson (1976) showed that if limited nutrition initially results in the runting of pigs before and after birth, high subsequent feed intakes do not result in normal development during compensatory growth, again implying that some form of intrauterine fetal reprogramming had occurred.

Based on the schematic representation of muscle fiber development shown in Figure 3, this led to the central hypothesis tested in a number of our recent studies, that "by detrimentally affecting placental size in early gestation, uterine crowding will also affect fetal organ development and the number and type of muscle fibers, analogous to the situation of IUGR in nutritionally challenged sows" (Town, 2004).

Preliminary data from an initial experiment involving analysis of fetal and placental weights at term, and associations with IUGR effects measured in the neonate, indicated that even when the number of conceptuses in the uterus does not significantly affect birth weight, crowding nevertheless results in measurable IUGR in the fetus (Town, 2004). In another study, unilateral oviduct ligation was used as a surgical approach to vary the number of fetuses developing in the uterus. Even though the uterine crowding observed was not at the level that probably occurs in existing commercial dam-line sows, a greater number of fetuses in the uterus resulted in measurable developmental changes. As shown in Figure 4, there were again effects of increasing numbers of conceptuses and fetuses in the uterus on placental development (Town et al., 2004b). Furthermore, in the same study, among the various measures of IUGR, we were able to establish specific effects on the estimated total number of secondary muscle fibers that were associated with differences in the wet weight and cross-sectional area of the semintendinosus muscle. This provides some of the first evidence that the variation in the number of conceptuses surviving to the postimplantation period will affect not only placental, but also fetal, development. In the literature cited earlier, comparable effects on muscle fiber development, created by maternal undernutrition during gestation, resulted in lifetime limitations in growth performance and muscle mass. It is thus reasonable to assume that the observed effects of embryo crowding in the uterus on the number of secondary muscle fibers will be associated with similar limitations in postnatal growth performance. The extent of uterine crowding that we have managed to create in the above study, and a number of comparable studies in both gilts and greater parity sows, has been less than the crowding we predict in at least a subpopulation of greater parity sows in existing commercial dam-lines (Vonnahme et al., 2002; Foxcroft and Town, 2004). Nevertheless, we appear to be able to demonstrate that differences in intrauterine crowding in the prenatal period in individual females have consequences for the pattern of fetal muscle fiber development. Furthermore, in embryonic tissues harvested from the sows reported in the study of Town et al.

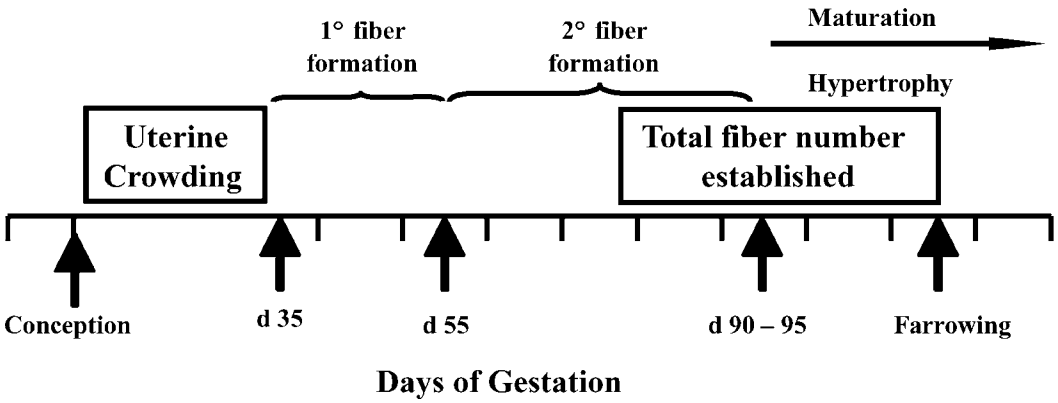

Figure 3. Schematic representation of the time-course of muscle fiber development in the pig, indicating a critical window in early pregnancy when crowding effects limit placental development and set in place detrimental effects on fetal development and lifetime growth performance.

(2004b), we have since been able to study the effect of moderate crowding on the expression of the myogenic regulatory factors *myogenin* and *myoD*. This study provided direct evidence that crowding at d 30 of gestation can impact the differentiation of muscle fibers through reductions in *myogenin* expression in this experimental paradigm, and, interestingly, most of the overall litter effect was found to originate from selective effects on *myogenin* expression in the male embryos in the litter (Tse, 2005). Together with the earlier literature reviewed above, these results support our earlier suggestion that environmental influences on embryonic and fetal development are likely an important component of the biological origins of the variability in postnatal growth performance encountered in the pork production industry (Foxcroft and Town, 2004).

IMPLICATIONS FOR DEVELOPING BETTER PRODUCTION SYSTEMS

Implications for Segregated Management of Grow–Finish Pigs

If prenatal development can have measurable effects on postnatal variation in growth performance, what are the possible practical resolutions to this problem? It is likely that certain categories of sows, such as high-parity sows with increased ovulation rates and few problems with lactational catabolism, will produce the greatest incidence of altered developmental potential due to overcrowding in the uterus. In extreme situations, developmental limitations will also be associated with low birth weights, and at least this population of

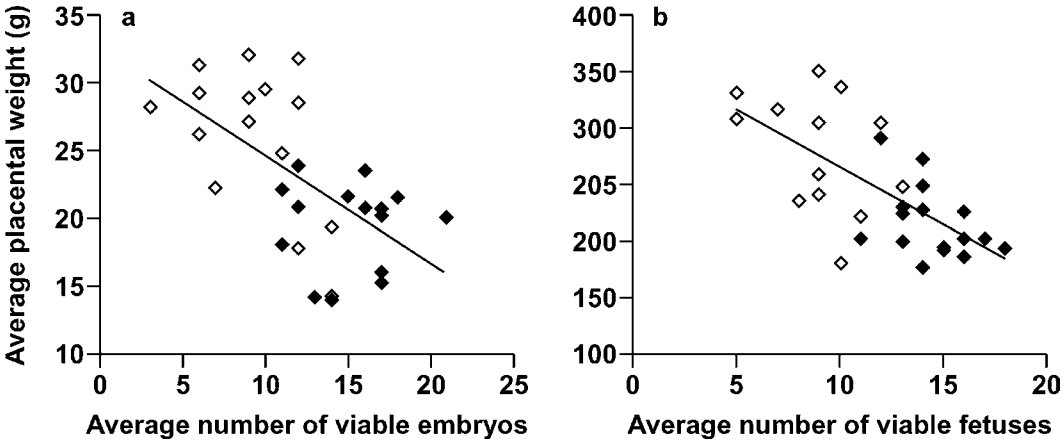

Figure 4. Correlation between average placental weight and a) number of viable embryos at d 30 of gestation (r = –0.61; $P = 0.0003$); and b) number of viable fetuses at d 90 of gestation (r = –0.67; $P < 0.0001$). Control (◇); unilateral oviduct ligated (◆) sows (From Town et al., 2004b).

pigs could be designated to segregated production flows at the nursery and grow-finish stages.

The information reviewed above also indicates that the growth potential of runt pigs within a litter will forever be compromised. Therefore, simply mixing these pigs with smaller weight pigs that were not the runts within their own litters does not recognize that the developmental potential of these two sets of pigs could be very different. Realistically, runts have little potential in traditional grow-finish systems competing unfairly with a succession of equal-weight pigs with which they are sorted during the production process. If we accept that runting and other forms of IUGR actually limit the number of muscle fibers, then it is probably unrealistic to consider that nutritional intervention can do much to alleviate this problem. Both muscle mass and meat quality at slaughter will be negatively impacted in runt pigs (see companion review of Rehfeldt and Kuhn, 2006). Use of expensive nutritional programs to try and correct this problem may not, therefore, be money well spent. Because other data indicate that the survivability of runt pigs may also be seriously compromised, special attention may be needed to keep runt pigs through the weaning and nursery stages of production.

Implications for Selection of Replacement Gilts as Terminal-Line Production Females

Paradoxically, in selecting gilts for terminal-line production when internal multiplication of replacement gilts occurs, managers must also be alert that low birth and weaning weights will tend to be inversely related to litter size born. There is longstanding evidence that the rate of sexual maturity and lifetime productivity of gilts raised in different-sized litters is adversely affected by postnatal growth performance (Nelson and Robison, 1976; van der Steen, 1985; Jorgensen, 1989). This impact of low birth weight from gilts born in large litters can be a major component of the effect of litter of origin in experiments in which littermates are allocated to different treatments and litter is included in the statistical analysis. It is not surprising, therefore, that several publications report effects of litter of origin on a whole range of biological and production characteristics when included in the analytical model (see Deligeorgis et al., 1984, 1985; Almeida et al., 2001). Furthermore, as discussed above, recent research suggests that the lower initial growth performance is very likely an imprinted effect due to competition in the uterus. In the most controlled selection systems, developed in collaboration with commercial producers, gilts born in gilt litters invariably weigh less than 1.5 kg at birth and are not selected as breeding herd replacements because of the anticipated effects of low birth weight on subsequent growth performance (C. Moore, Robitaille Farms, Quebec, Canada; personal communication).

Table 2. Production data recorded for individual hyperprolific white-type sows from commercial units in Brittany, France[1]

Sow parity	Total pigs born	Pigs born dead	Pigs born live	Adjusted litter size 48 h after farrowing
7	**20**	**6**	**14**	**12**
2	15	2	13	13
5	**19**	**5**	**14**	**11**
2	15	1	14	11
9	14	1	13	12
5	13	0	13	12
4	19	1	18	13
2	12	0	12	12
5	13	1	12	10
5	18	0	18	11
4	16	1	15	12
1	10	2	8	12
4	16	0	16	12
5	**18**	**3**	**15**	**11**
8	**22**	**5**	**17**	**11**
5	**13**	**7**	**6**	**12**

[1]Individual greater parity sows (data shown in bold) show both an increase in total and dead born pigs per litter. Data are from personal communication (P. Leveneau, ISPAIA, France).

Implications for the Use of Hyperprolific Sows for Increasing Litter Size Born

Given the impact of an imbalance among ovulation rate, embryonic survival, and uterine capacity on fetal and postnatal development, the reproductive characteristics of prolific dam-lines whose genes are incorporated into the breeding nucleus with the intention of improving the overall productivity of terminal-line sow need careful consideration. Thus, although the primary goal of increasing the number of pigs born per litter may be achieved, data from some of these prolific dam-lines leads us to suggest that many of the adverse prenatal programming effects associated with inadvertent crowding of fetuses in the uterus may be prevalent in the mature sows in these populations. A consideration of the proportion of live-born vs. dead-born pigs within the litters of one population of hyperprolific French sows (see Table 2) suggests that the growth potential of the live-born pigs that survive to weaning will have been seriously compromised by intrauterine competition with an increasing number of fetuses that are born dead. This conclusion is supported by data shown in Table 3, from this same population of sows, showing the relative birth weight of pigs born in different-sized litters. We are presently investigating the reproductive characteristics of a similar line of hyperprolific French sows being imported into Canada. Preliminary data (J. R. Harding, WCVM, University of Saskatchewan, Canada, personal communication) confirm that in the greater parity sows in this population, high ovulation rates can be associated with substantial crowding of viable conceptuses at d 30 of gestation, with obvious

Table 3. Effect of litter size at birth on the average birth weight of pigs born to the hyperprolific white-type sows in commercial production in France, for which data are shown in Table 2[1]

Number of pigs in the data set	Average total pigs born	Average birth wt, kg	Percentage of pigs within specific weight ranges			
			<1.0 kg	1.0 to 1.5 kg	1.5 to 2.0 kg	>2.0 kg
2,637	12.6	1.49	7	37	43	13
432	17.4	1.27	15	57	26	2

[1]Data are from personal communication (P. Leveneau, ISPAIA, France, 2002–2003).

implications for deleterious effects of prenatal programming on postnatal performance.

The hyperprolific Chinese breeds, of which the Meishan has been most widely incorporated into synthetic dam-lines currently in commercial use, offer an interesting comparison to the hyperprolific white-type maternal lines developed from French populations. Accumulated evidence suggests that the increase in functional uterine capacity results in greater number of pigs born per litter as a consequence of increased placental efficiency in the Meishan. However, because the physical capacity of the uterus is not different, this dictates that the birth weight of Meishan pigs at term is lower than in the less prolific white breeds. A critical question is whether this lower birth weight is associated with limitations in muscle fiber numbers, which is indicative of prenatal programming as described for fetuses developing in the relatively crowded uterus of a white-type dam. Alternatively, if the greater efficiency of the Meishan placenta is able to provide sufficient nutrients to the conceptus in the critical early postimplantation period, then the process of myogenesis may not be as affected as it would be in a white-type dam with the same number of conceptuses in the uterus. If this were the case, then the lower birth weight might be partly compensated by a greater potential for postnatal compensatory growth.

Clearly, a better understanding of the characteristics of specific hyperprolific dam-lines is needed. This information, and an increasing focus on the need to maximize total net revenues per sow in terms of the value of saleable pork products, relative to the input costs involved per kilogram of pork sold, should allow the most commercially acceptable terminal-line dams to be developed in the future. Ultimately, as in the case with the UHO experimental paradigm, selection of sows with increased uterine capacity offers the best opportunity for increasing the number of pigs born per litter without compromising the postnatal growth performance of these pigs. Perhaps at a population level, selection for litter size needs to include data from multiparous sows, with birth weight being used, in additional to litter size, as a means of identifying sows in which the dynamics of prenatal loss does not result in detrimental prenatal programming effects on postnatal growth potential.

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