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Fetal Erythropoiesis and Other Factors which Influence Uterine Capacity in Swine

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Large litter size of healthy piglets at weaning is an important aspect of swine production efficiency. this is influenced by several factors like ovulation rate, fertilization rate, early embryonic mortality and utrine capacity. Several studies showed that none of the single trait is effective to influence the production efficiency. Genetic selection in association with hormonal manipulations to reduce placental size and increase its efficiency has been found effective. The uterine capacity is also inproved through the improvement of fetal erythropoiesis during early as well as late gestation due to use of genetic selection, marker assisted selection or other treatments. Increased uterine capacity may be useful for increasing litter size when treatments are applied for increasing the number of available embryos either by increasing ovulation rate and decreasing embryonic mortality or transfer of viable embryos.

Key words: Uteroferrin, folate, placenta, uterus.

Introduction

An important component of the efficiency of swine production is the number of piglets produced per sow year. This depends on litter size

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at each farrowing and the interval required to re-establish pregnancy in the sow after farrowing. Factors influencing litter size of swine include ovulation rate, fertilization rate, early embryonic mortality (embryonic loss occurring before day 30 of gestation) and uterine capacity (the number of fetuses the uterus can maintain until farrowing (Leymaster *et al.*, 1986; Christenson *et al.*, 1987; 1993). Ovulation rate can be modified using genetic selection (Johnson *et al.*, 1984) or hormonal treatment (Day *et al.*, 1967; Dziuk, 1968; Longenecker and Day, 1968). However, increased ovulation rate does not result in an increase in litter size equal to the increase in potential embryos. Fertilization rates have been reported to be high (90 to 95%) in domestic species including the pig (Polge, 1978), indicating that fertilization rate does not limit litter size. Early embryonic mortality has been estimated at 20 to 40% in swine (Hanly, 1961; Perry and Rowlands, 1962) and under normal conditions, early embryonic mortality is a major factor governing litter size. However, most studies in which the number of potential embryos is increased, either by increasing ovulation rate or increasing the number of embryos by embryo transfer, report increased number of embryos surviving to day 30 (Day *et al.*, 1967; Longenecker and Day; 1968; Bazer *et al.*, 1969b; Pope *et al.*, 1972). Thus, increasing potential embryos by embryo transfer or by increasing ovulation rate using selection or hormonal manipulation can be used to overcome the negative effect of early embryonic loss on litter size. Unfortunately, the extra embryos present on day 30 of gestation are subsequently lost prior to farrowing (Bazer *et al.*, 1969a;b; Johnson *et al.*, 1984). These results indicate that with currently available technology, the limit to litter size in swine is due to uterine capacity.

Evidence suggests that numerous uterine, placental and fetal factors all contribute to the number of conceptuses the uterus can support to term. Thus, increased uterine capacity may be obtained by changing the function of each of these components. Furthermore, because each component interacts with the other components, changes in one component may result in beneficial changes in the other two. The results of several studies using various model systems suggest clues to beneficial changes in uterine, placental and fetal traits that may yield increased uterine capacity.

The uterus and uterine capacity

The most obvious aspect of the uterus which might be modified to increase uterine capacity is its size. Chen and Dzuik (1993) reported that a large variation exists in the length of the uterine horns among gilts. Length of the uterus is also correlated to litter size (Wu *et al.*, 1987; Wu and Dziuk, 1995) and approximately 20 cm of initial uterine length is required for normal conceptus development (Chen and Dziuk, 1993). Because of the large variation in uterine length, genetic selection for uterine length could be a successful means of increasing uterine capacity. This concept is further supported by the report that heritability of prepubertal uterine length is high (h^2=.5; Young *et al.*, 1996). Furthermore, a genetic correlation of .64 was estimated between prepubertal uterine length and uterine capacity, while the phenotypic (overall) correlation between prepubertal uterine length and uterine capacity was .16, within a group of gilts selected for uterine capacity using litter size after unilateral hysterectomy-ovariectomy (UHO) as a measure of uterine capacity (Christenson *et al.*, 1987; Young *et al.*, 1996). The low phenotypic correlation between prepubertal uterine length and uterine capacity is likely due to variation in growth of the uterus during puberty, as well as large random/environmental variation in uterine capacity. The large random/environmental variation in uterine capacity is reflected by the low repeatability of this trait within a gilt (approximately .2; J.L. Vallet, unpublished observations). Nevertheless, the strong genetic correlation between prepubertal uterine length and uterine capacity combined with the high heritability of prepubertal uterine length suggests strongly that selecting for increased uterine length is a means whereby uterine capacity of swine may be increased (Young *et al.*, 1996).

The literature also suggests that changes in uterine function independent of changes in uterine length can have a beneficial effect on uterine capacity. The best demonstration of this concept comes from studies of the Meishan pig, which has been extensively studied due to the superior fertility of this breed. To maintain larger litter sizes, the Meishan breed must possess greater uterine capacity than European breeds of pigs. Results of several experiments suggest that a major component of the greater uterine capacity of this breed is decreased

growth of the placenta and fetus (Christenson, 1993; Ford, 1997; Biensen *et al.*, 1998) allowing more conceptuses to be accommodated by the uterus. During early pregnancy, blastocysts developing in a Meishan uterus grow more slowly, elongate at fewer cells and to a lesser extent than blastocysts developing in a European breed uterus (Anderson *et al.*, 1993; Rivera *et al.*, 1996; Wilson and Ford, 1997; Biensen *et al.*, 1998). At day 30 of pregnancy, Meishan or European breed embryos gestated in the uterus of a Meishan gilt resulted in smaller conceptuses than when gestated in the uterus of a York gilt and no significant effect of the breed of conceptus was reported (Ford *et al.*, 1994; Youngs *et al.*, 1994). At day 90 of gestation, placental weights were less when embryos of either breed were gestated in uteri of Meishan gilts than in York gilts. Again, there was no influence of the breed of the conceptus on placental weight (Wilson *et al.*, 1998). Fetal weights were also less when embryos of either breed were gestated in uteri of Meishan gilts compared to York gilts. An effect of the breed of the conceptus was found for fetal weight only for embryos gestated in uteri of York gilts. Finally, at term, Meishan embryos gestated in uteri of York gilts had smaller placentae but similar fetal weights compared to York embryos. A similar comparison for embryos gestated in uteri of Meishan gilts was not made (Wilson *et al.*, 1998). Taken together, these results suggest that up to day 90 of gestation, most of the differences in the growth of the Meishan fetus and placenta compared to European breeds is dependent on the breed of the uterus (i.e., a uterine dependent phenomenon). From day 90 to term, the breed of the conceptus also plays a role in placental and fetal growth.

Comparison of the uterine lumenal contents of Meishan and European breed gilts during the period of blastocyst growth and elongation indicates that the Meishan uterus secretes less total protein, uteroferrin, retinol binding protein (Bazer *et al.*, 1991; Ford and Youngs, 1993; Vallet *et al.*, 1998b), and insulin like growth factor-1 (IGF-1; Wilson and Ford, 1997) resulting probably in the slower growth of blastocysts gestated in this environment. Taken together, these results indicate that differences in uterine function between Meishan and European breeds influence the size of placenta and fetus, thereby affecting uterine capacity.

Placental function and uterine capacity

At a given placental weight, placental function may also influence uterine capacity. Meishan placentae have been reported to be more vascular than placentae from European breeds (Biensen *et al.*, 1998; Wilson *et al.*, 1998) and it has been hypothesized that this allows the Meishan fetus to survive attached to a smaller placenta. However, the need for an increase in placental function to abrogate the smaller size of the Meishan placenta is lessened due to the smaller fetus in the Meishan for most of gestation (Christenson, 1993; Ford *et al.*, 1994; Wilson *et al.*, 1998), although whether Meishan foetuses are smaller at birth is controversial (Wilson *et al.*, 1999). Less nutrients are likely to be required to maintain a smaller fetus. Furthermore, it is not yet clear whether the observed increased vascularity of the Meishan placenta is a property of Meishan placentae or simply a function of the reduced size of the Meishan placenta. It is not known whether decreasing placental size in European breeds (e.g., using UHO or some other technique to crowd the conceptus) would generate placentae of the same size and vascularity as Meishan placentae. Most recently, it has been reported that the Meishan placenta produces more vascular endothelial growth factor (VEGF; Vonnahme *et al.*, 1999), a protein which plays a role in controlling the vascularity of tissues. If the changes in vascularity of the Meishan placenta are a result of modified placental development, increased VEGF and other factors controlling vascularization are likely responsible.

Results indicating that the Meishan placenta may be more vascular than placenta from European breeds have led to the introduction of the concept of placental efficiency (Wilson *et al.*, 1999). Placental efficiency for a given conceptus has been defined as the weight of the fetus divided by the weight of the placenta and is interpreted to indicate the g of fetus which can be supported per g of a given placenta. A portion of placental efficiency is thought to be the degree of vascularization of the placenta and recent reports indicate a correlation between the two traits (Vonnahme *et al.*, 1999). Selection for placental efficiency led to improvements in litter size, suggesting that selection successfully modified uterine capacity in the selected groups (Wilson *et al.*, 1999). However, the calculation of placental efficiency assumes that for all

conceptuses, the weight of the fetus is controlled primarily by the availability of nutrients from the placenta. This is unlikely to be true because the foetus likely has its own internal mechanisms regulating fetal growth. Regression analysis of the relationship between fetal weight and placental weight measured at 105 days of gestation in a population of 1/2 Meishan, 1/2 white crossbred unilaterally hysterectomized-ovariectomized sows indicates that the relationship is curvilinear (Fig. 1a; $p<0.0001$). In fact, there is no relationship between fetal weight and placental weight for placentae greater than 200 g. Furthermore, the funnel shape of the distribution around the regression line (Fig. 1a) indicates that the variance in fetal weight increases as placental weight increases. These data suggest that at low placental weights, where placental transport is limiting, fetal weight is a more reliable measure of placental efficiency than at high placental weights. Placentae greater than 200 g are likely to be able to transfer more nutrients than are required by the developing fetus. The increased variance in fetal weights as placental weight increases may be partially due to the increasing influence of fetal genes or external environmental factors which influence fetal growth. These genes and environmental factors may have limited effect when placental size is limiting. The curvilinearity of the relationship in Fig. 1a indicates that as the size of the placenta increases, placental efficiency falls, resulting in the negative correlation between placental weight and placental efficiency reported previously by Wilson *et al.* (1999) and illustrated using our own more extensive data in Fig. 1b. Thus, selection on the basis of placental efficiency is also selection on the basis of placental size, because the two are correlated. Because placental size alone can influence uterine capacity and litter size, it is unclear whether the changes in litter size obtained by selection for placental efficiency, as reported by Wilson *et al.* (1999), were due to changes in placental efficiency or simply changes in placental size. As indicated above, vascular density may also change with placental size. The observed correlation between placental vascularity and placental efficiency may be due to the fact that both are correlated with placental size. Despite these criticisms, the concept of Wilson *et al.* (1999) that placentae differ in their ability to maintain fetuses is supported by the variation around the regression line for placentae weighing less than 200 g (Fig. 1a). It

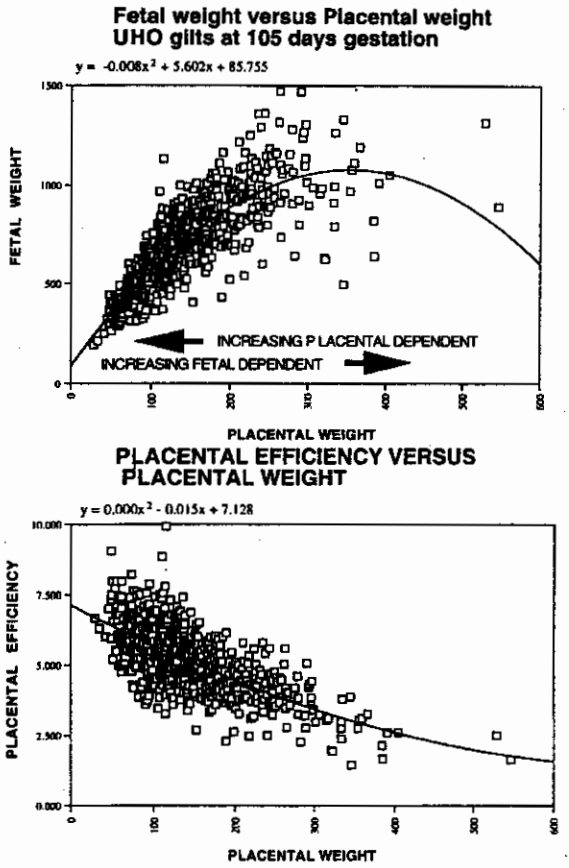

Fig. 1: Scatterplots of the relationship between fetal weight and placental weight (a) and between placental efficiency (fetal weight/ placental weight) and placental weight (b) are illustrated. Data were collected on day 105 of gestation from 1/2 Meishan, 1/2 White crossbred gilts that had previously undergone unilateral hysterectomy-ovariectomy. Both relationships were curvilinear. No relationship between fetal weight and placental weight for placentae weighing more than 200 g was observed.

is clear that when placental weights are low and placental support is limiting; for any given placental weight, fetal weights differ. Collectively, the observations of Wilson *et al.* (1999) along with those illustrated in Fig. 1a suggest that variation in placental efficiency exists and could be exploited to improve uterine capacity. Although selection for placental efficiency while placing a lower limit on fetal weight, as performed by Wilson *et al.* (1999), partially alleviates some of these problems, the graph in Fig. 1a suggests that a more efficient way to select gilts for differences in placental efficiency than that used previously might be to select animals above and below the regression line that defines the relationship between fetal and placental weight. However, this selection should be done at a point along the regression line where there is still

a strong relationship between fetal weight and placental weight (i.e., below 200 g placental weight). Furthermore, because placental efficiency has a greater influence on fetal weight as placental weight decreases, selection should be made at as low a placental weight as possible.

The influence of the fetus on uterine capacity

From the above discussion, it is clear that aspects of fetal growth and development can also influence uterine capacity. Simply slowing the overall fetal growth rate, which appears to occur in the Meishan breed for most of gestation (Christenson, 1993; Biensen *et al.*, 1998; Wilson *et al.*, 1998), decreases the demand for nutrients that must be delivered by the uterus and placenta and likely improves survival. However, the growth and development of the fetus does not occur at a uniform rate during pregnancy. Thus, depending on what functions are occurring within the fetus, the demands of the fetus for various nutrients are likely to change throughout development. There may be sensitive periods in which particular aspects of swine fetal development require specific nutrients in order to occur appropriately and efficiently.

The existence of such sensitive periods is indicated by several experiments in which intrauterine crowding was induced using a variety of methods. Knight *et al.* (1977) used UHO to increase crowding among conceptuses and reported the resulting litter size in groups of gilts throughout gestation. Litter size and fetal survival were maintained up to day 30, but fetuses were lost by day 40 of gestation (Table 1). Vallet and Christenson (1993) crowded conceptuses by uterine ligation and then determined conceptus survival within the crowded and roomy uterine environments on day 25 and 35 of gestation. On day 25, there was no effect of crowding on fetal survival. By day 35, conceptus survival was significantly reduced in the crowded uterine horns. Chen and Dzuik (1993) examined conceptus survival at various days during early pregnancy after limiting conceptuses to different amounts of uterine space using uterine ligation. Severe limitation of uterine space resulted in significant loss of conceptuses at all days examined. However, when uterine space limitations were more moderate, a 20% decrease in survival of conceptuses between day 29 and day 35 of pregnancy was evident. An assessment of reports in which intrauterine crowding was

Table 1
Summary of experiments examining the effect of uterine crowding on litter size and fetal survival

Authors	Methods to increase embryos	Day of gestation	Effect on litter size	Effect on fetal survival
Day *et al.*, 1967	superovulation	25	+1.0 to +1.6	-27%
Longenecker and Day, 1968	superovulation	25	+4.9	-16%
		40	+5.6	-16%
Dziuk, 1968	superovulation	18-100	-	+5%
	embryo transfer		+4.1	-
Bazer *et al.*, 1969a	embryo transfer	90	-0.3	-33 to -53%
Bazer *et al.*, 1969b	embryo transfer	25	+2.4	-24%
		105	+0.2	-33%
Pope *et al.*, 1972	embryo transfer	26-29	+9.5	-1%
Johnson *et al.*, 1984	selection	30	+2.3	-5%
		70	+0.8	-11%
Johnson *et al.*, 1999	selection	50	+3.8	-4%
		farrowing	+1.1	-
	Methods to decrease uterus			
Dziuk, 1968	UHO	18-100	-2.6	-8%
	Uterine ligation		-	+5%
Fenton *et al.*, 1970	UHO	25	-0.6	-8%
		105	-4.1	-32%
Knight *et al.*, 1977	UHO	20	-0.3	+1%
		25	-0.7	-12%
		30	+0.7	+8%
		35	-2.0	-7%
		40	-4.5	-41%
		50	-0.3	-14%
		60	-2.0	-18%
		70	-3.2	-30%
		80	-4.5	-42%
		90	-3.8	-11%
		100	-0.5	-18%
Christenson *et al.*, 1987		UHO	86	-2.7 -19%
			farrowing	-3.3 -29%
Huang *et al.*, 1987	UHO	30	-1.4	+1%

Wu *et al.*, 1989	uterine ligation	20 (5 cm/CL)	-	-21%
		25 (5 cm/CL)	-	-60%
		50 (5 cm/CL)	-	-81%
		50 (10 cm/CL)	-	-52%
		50 (20 cm/CL)	-	-38%
		50 (30 cm/CL)	-	-11%
Chen and Dzuik, 1993	uterine ligation	17 (5 cm/CL)	-	-54%
		23 (5 cm/CL)	-	-58%
		29 (5 cm/CL)	-	66%
		35 (5 cm/CL)	-	-77%
		41 (5 cm/CL)	-	-71%
		17 (5 cm/CL)	-	-22%
		23 (15 cm/CL)	-	-14%
		29 (15 cm/CL)	-	-33%
		35 (15 cm/CL)	-	-54%
Vallet and Christenson, 1993	uterine ligation	25	-	-16%
		35	-	-67%
Vallet and Christenson, 1994	UHO	45	-3.8	-24%
Vallet *et al.*, 1994	uterine ligation	40	-	-71%
		60	-	-18%
		80	-	-36%
Vallet and Christenson, 1996	UHO	45	-2.4	-21%
Pearson *et al.*, 1998	UHO	24	+0.5	+0.5
		30	-2.5	-7%
		40	-4.1	-18%
Vallet *et al.*, 1999c	UHO	35	-2.8	-17%

accomplished by a variety of means (UHO, uterine ligation, superovulation, embryo transfer, Table 1) indicates that in most cases, conceptus survival in crowded uterine environments is high previous to day 30 and is impaired by day 35 to 40. The discreteness of the incidence of conceptus loss due to intrauterine crowding suggests that some aspect of development is occurring during this period that is unusually sensitive to the effects of crowding.

Evidence of a second period near farrowing in which the fetus appears to be sensitive to intrauterine crowding also exists. Christenson *et al.* (1987) reported that about 1/3 of the fetal losses that will occur

in UHO gilts occurs from day 86 to farrowing. Selection of pigs for an index of ovulation rate and embryo survival at day 50 resulted in significant improvements in litter size at day 50 of gestation, but the increase in litter size at farrowing was much less than at day 50 (Johnson *et al.*, 1999). Finally, in several experiments in which fetuses in UHO gilts were examined at 105 days of gestation, many fetuses which have either recently died or appear likely to die prior to or during farrowing have been observed (J.L. Vallet, unpublished observations).

Several changes in uterine, placental and fetal function and development occur between day 30 and 40 of gestation. Uteroferrin and total protein secretion by the endometrium increases dramatically (Geisert *et al.*, 1982; Zavy *et al.*, 1984; Bazer *et al.*, 1991; Vallet *et al.*, 1996) as does uterine blood flow (Ford and Christenson, 1979; Ford, 1995). The placenta essentially matures during this period (Perry, 1981; Bazer, 1989) going from an apparently simple structure made up of a thin membrane, hyaluronic acid gel and blood vessels to a more complex structure that includes areolae; specialized sites that are involved in the transport of uteroferrin and other uterine gland products to the conceptus (Raub *et al.*, 1985). Organ systems which provide vital functions within the fetus during this period include the heart, kidney and liver. The influence of intrauterine crowding on blood flow to the uterus has not been investigated. However, there appears to be no influence of intrauterine crowding on uterine protein secretion (Vallet and Christenson, 1993; 1994). Furthermore, little change in the relationship between the endometrium and the placenta is likely to occur as intrauterine crowding increases, so a decrease in the availability of uterine products required for placental function and development is unlikely to be the root cause of fetal losses due to intrauterine crowding. Of the functioning organ systems, there is no evidence that the function of the heart and kidney change dramatically during this period. In contrast, the liver becomes a major site of fetal erythropoiesis at about this time (Ducsay *et al.*, 1982; Fig. 2).

Fetal erythropoiesis coincides with fetal loss due to intrauterine crowding

On day 24 of pregnancy, fetal red blood cells are all nucleated. The predominant circulating cells (80-90%) are polychromatic erythroblasts,

immature cells of the erythropoietic lineage. By day 30, about 70% of the circulating cells remain nucleated and are 1/3 polychromatic erythroblasts and 2/3 orthochromatic erythroblasts. The nonnucleated cells that are present are predominantly reticulocytes. By day 40, 60-70% of the circulating cells are mature erythrocytes. Coincident with these changes is a dramatic (10-fold) increase in the concentration of circulating red blood cells in the fetal blood. About this same time, fetal red blood cell precursors become resident within the fetal liver (Fig. 2). Thus, the period between day 30 and 40 of pregnancy coincides with the development and rapid expansion of the fetal blood supply (Pearson *et al.*, 1998).

Interestingly, changes in blood iron levels which could have a negative impact on fetal erythropoiesis are coincident with the second period of fetal loss occurring in late gestation. Plasma levels of both transferrin and uteroferrin fall in late gestation, even though uteroferrin production by the endometrium remains high (Vallet *et al.*, 1996). It is possible that the requirement for iron by the developing fetus during late gestation is greater than the amount of iron the uterus is capable of providing during late gestation. It is well known that newborn pigs are iron deficient (Ullrey *et al.*, 1960). Uterine crowding may make this situation worse and the iron deficiency could become severe enough to compromise the health of the fetus before or during farrowing.

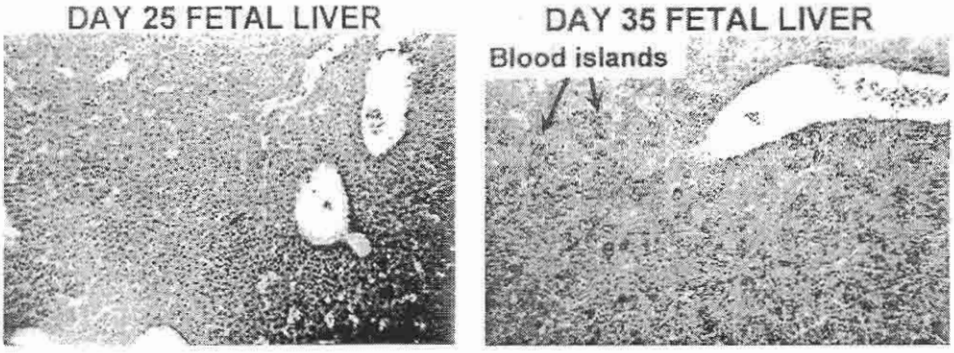

Fig. 2: Representative hematoxylin and eosin stained sections of fetal liver collected on days 25 and 35 of pregnancy are illustrated. Note the dramatic increase in the presence of blood islands in the fetal liver on day 35.

Fetal erythropoiesis requires specific uterine products

Efficient erythropoiesis requires iron, folate, vitamin B12 and erythropoietin (Shane and Stokstad, 1985; Fried, 1995; Fisher, 1997). Iron is provided to the fetus by the secretion of uteroferrin (Roberts *et al.*, 1987; Roberts and Bazer, 1988) by the endometrium. Uteroferrin is a 35,000 Mr protein which contains two irons (Schlosnagle *et al.*, 1974). It exists in two forms within the uterine environment, a purple and a pink form, depending on the redox state of the diiron center (Schlosnagle *et al.*, 1976). Secretion rates of uteroferrin by the endometrium increase dramatically between day 10 and 13 of pregnancy and again between day 20 and 40 of pregnancy and then remain high at least to day 90 of gestation (Basha *et al.*, 1979; Geisert *et al.*, 1982; Zavy *et al.*, 1984; Bazer *et al.*, 1991; Vallet *et al.*, 1996; 1998b). What controls the timing of the secretion of uteroferrin is not well understood. The changes in protein production are in part driven by changes in mRNA levels (Simmen *et al.*, 1988). The increase in uteroferrin that occurs from day 10 to day 13 of gestation is predominantly controlled by biochemical events associated with prolonged exposure to progesterone and is modulated by the conceptus, possibly via the secretion of estrogen (Vallet *et al.*, 1998b). It has been suggested that the increase that occurs during later pregnancy (day 20 to 40) is controlled by changes in the progesterone to estrogen ratio. Progesterone concentrations decline during this period. Estrogen production by the placenta peaks at day 30 and then decreases until day 60, after which, estrogen production rises to term (Knight *et al.*, 1977). The presence of the conceptus is associated with an increase in uterine protein production (Basha *et al.*, 1980; Vallet and Christenson, 1994; 1996). However, treatment of pregnant or pseudopregnant pigs with estrogen does not duplicate the effect of the presence of the conceptus (Vallet and Christenson, 1994; 1996). Thus, the maternal and conceptus factors regulating the rise in uteroferrin secretion require further investigation.

Uteroferrin is a product of the deep uterine glands (Chen *et al.*, 1975; Fazleabas *et al.*, 1985) and, once secreted, is picked up by the placental areoloe (Renegar *et al.*, 1982; Raub *et al.*, 1985). It is unclear what happens to the uteroferrin within the placenta. Studies using ^{59}Fe indicate that much of the iron remains within the placenta (Ducsay *et*

al., 1982), perhaps in the form of ferritin (Theil, 1987). Thus, a portion of the uteroferrin is likely degraded within the placenta and the iron is either stored or resecreted in association with transferrin (Huebers and Finch, 1987). Some of the uteroferrin escapes the placenta and can be measured in the fetal blood, although concentrations are low (Renegar *et al.*, 1982; Vallet *et al.*, 1996). Receptors for the carbohydrate attached to uteroferrin (Baumbach *et al.*, 1991) are present on the reticuloendothelial cells of the fetal liver (Saunders *et al.*, 1985; Michel *et al.*, 1992), thus providing a mechanism whereby the liver can obtain iron directly from uteroferrin. The fetal kidney also clears uteroferrin from the fetal blood stream, releasing the intact uteroferrin into the allantoic sac. The allantoic fluid contains high concentrations of uteroferrin after day 40 of gestation (Bazer *et al.*, 1974; Vallet *et al.*, 1996) thus, the fetal kidney shunts uteroferrin into the allantoic sac against a large concentration gradient. Within the allantoic sac, uteroferrin gives up its iron to transferrin and the transferrin can reenter the fetus (Buhi *et al.*, 1982; 1983). Uteroferrin cannot reenter the fetus from the allantoic sac. The metabolism of uteroferrin in this way is likely an evolutionary adaptation to the chemical characteristics of iron and uteroferrin. Free iron catalyzes lipid oxidation in the presence of oxygen. This is normally controlled by transferrin, which binds iron tightly enough to inhibit this reaction (Huebers and Finch, 1987). In contrast, iron bound to uteroferrin has enhanced reactivity compared to free iron (Vallet, 1995), probably due to the redox activity of the diiron center. Maintenance of low uteroferrin concentrations within the plasma; shunting of uteroferrin into the allantoic sac, which is a low oxygen environment away from vital fetal organs; and the transfer of iron to transferrin are all mechanisms that protect the fetus from uteroferrin induced lipid oxidation. Further proteins that counteract the lipid oxidizing activity of uteroferrin include the uteroferrin associated proteins and retinol binding protein. The uteroferrin associated proteins bind the pink, oxidative form of uteroferrin (Baumbach *et al.*, 1986; Murray *et al.*, 1989) and prevent lipid peroxidation (Vallet, 1995). Retinol binding protein provides antioxidant activity (Vallet *et al.*, 1995).

Folate transport is likely to be accomplished through the interaction of two recently discovered endometrial folate binding proteins (FBP),

a secreted form and a membrane bound or receptor form (Vallet *et al.*, 1999e). The molecular weight of the secreted FBP is about 30,000, the membrane form has not been characterized (Vallet *et al.*, 1998a). Uterine production of the secreted form increases dramatically between day 10 and 13 of the cycle or pregnancy (Vallet *et al.*, 1998a; 1999a). The timing of the increase is a function of prolonged exposure to progesterone, similar to that of uteroferrin, but does not appear to be influenced by the presence of the conceptus (Vallet *et al.*, 1999a). The increase in uterine production of secreted FBP occurs in the absence of changes in the amount of mRNA for this protein within the endometrium, suggesting that changes in translation of the mRNA may account for the increase in production rate (Vallet *et al.*, 1999e). The 5' untranslated region of the cDNA for this protein is heterogeneous; however, reverse transcription polymerase chain reaction analysis of endometrial mRNA for the different 5' untranslated regions does not appear to explain the changes in production of the protein (Fig. 3). The mRNA for the membrane FBP is present in both endometrium and placenta (Vallet

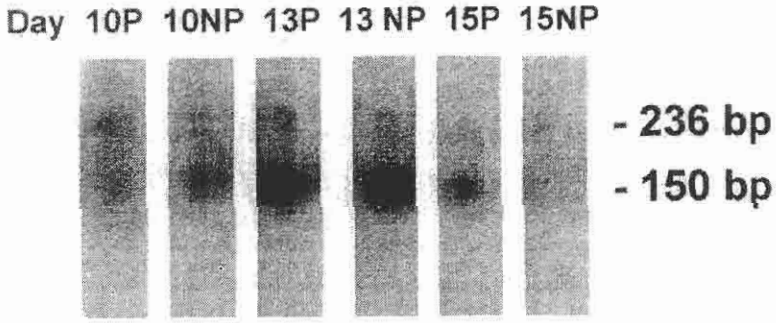

Fig. 3: Reverse transcriptase polymerase chain reaction analysis of the 5' untranslated region (UTR) of the secreted FBP gene during the cycle and pregnancy is illustrated. The upper and lower bands originate from 5'-UTR containing or lacking a differentially spliced region of the cDNA (Vallet *et al.*, 1999e). No consistent changes in the relationship of the two bands occurred during the cycle or pregnancy, suggesting that the relative proportion of mRNA with and without the differentially spliced region does not change during this period. The reverse transcription reaction was performed using the primer 5'AGGAGCACGAAAGAGCGTC3'. The polymerase chain reaction was performed using the primers 5'GGTCCGGAGAGGTGGTG3' and 5'CCAGGCCATGTTTGATCCAC3' as forward and reverse primers, respectively.

et al., 1999e). The 5' untranslated region of this cDNA was also heterogeneous. The gene for secreted FBP spans about 6 kb and contains 6 exons (Vallet *et al.*, 1998c). The gene for membrane FBP is larger (about 9 kb) and also contains 6 exons (J.L. Vallet, unpublished). The exon-intron patterns of the two genes are similar although the sizes of the introns in the two genes differ. The different 5' untranslated regions of membrane FBP suggest that two promoter regions may be present within this gene, similar to that found for the folate receptor in humans (Elwood *et al.*, 1997). Putative promoter elements have been suggested for the secreted FBP gene using the computer program signal scan (Vallet *et al.*, 1998c), but the actual promoter elements controlling these genes have yet to be explored.

Very little information on the mechanism of vitamin B12 transport to the developing conceptus is available. Pearson *et al.* (1998b) showed that mRNA for a haptocorrin-like protein is present in endometrium and the amount of mRNA for this protein changes with length of gestation. Haptocorrin is a vitamin B12 binding protein involved in transport of vitamin B12 in the gut (Hewitt *et al.*, 1990). Its role in vitamin B12 transport to the swine conceptus during pregnancy and the possible role of other factors in vitamin B12 transport require further study.

In most species, the dominant site of fetal erythropoietin production is the fetal liver (Zanjani *et al.*, 1977; 1981) although the placenta in humans also produces it (Conrad *et al.*, 1996). In the pig, both the fetal liver and the placenta contain mRNA for erythropoietin (Klemcke *et al.*, 1998). Counterintuitively, the amount of message for erythropoietin in the fetal liver decreases from day 24 to day 30 of pregnancy (Klemcke *et al.*, 1998). Blood concentrations of erythropoietin also decrease (Pearson *et al.*, 1998a). However, the expression of erythropoietin receptor mRNA within the fetal liver increases dramatically at the same time (Pearson *et al.*, 1998c) likely due to the increase in residence within the liver of red blood cell precursors, which have the receptor for erythropoietin on their cell surface. Thus, the increase in proximity of the erythropoietin receptor containing cells to the source of the erythropoietin may explain the decrease in fetal liver erythropoietin mRNA. Alternatively, as the red blood cell population matures during

this period, oxygenation of the conceptus is likely to improve. Adult erythropoietin production is controlled primarily by oxygen availability (Fried *et al.*, 1995). It is unclear whether this mechanism functions within the fetus, but if it does, the improvement in oxygen delivery caused by the maturation of the blood supply may explain the fall in erythropoietin mRNA within the fetal liver and the fall in erythropoietin concentrations in the blood.

Effect of intrauterine crowding on fetal erythropoiesis

Fetal erythropoiesis is a good candidate for a physiological mechanism that may be adversely affected by intrauterine crowding because dramatic changes in fetal erythropoiesis occur coincident with both major periods of fetal loss (Pearson *et al.*, 1998a; Vallet *et al.*, 1996) and efficient fetal erythropoiesis is dependent on secretion of the appropriate substrates by the uterus. Pearson *et al.* (1998) and Vallet *et al.* (1999c) examined the effects of intrauterine crowding on various aspects of fetal erythropoiesis from day 24 to 40 of pregnancy. These reports also compared fetal erythropoiesis in the prolific Meishan breed with that of white crossbred pigs. Positive correlations between hematocrit and fetal weight and hemoglobin and fetal weight were observed. Intrauterine crowding decreases fetal size, due to reductions in the size of the placenta (Knight *et al.*, 1977; Vallet and Christenson, 1993). Thus, intrauterine crowding resulted in more small fetuses which, in turn, had impaired erythropoiesis. These experiments further suggested that the blood supply of Meishan fetuses matured more rapidly than the blood supply of white crossbred fetuses. The rate of maturation of the blood supply in the Meishan may improve oxygen transport during this critical period of development and contribute to the enhanced fertility of this breed.

Deleterious effects of intrauterine crowding on fetal erythropoiesis during pregnancy have also been observed. Hematocrits, plasma iron, placental weights, fetal weights and fetal liver weights were measured in a large group of 1/2 Meishan, 1/2 white crossbred UHO gilts killed at 105 days of gestation. Positive correlations between hematocrit and placental, fetal and fetal liver weights and between plasma iron and placental, fetal and fetal liver weights were observed, similar to those

found during early pregnancy (Vallet *et al.*, 1999d). Thus, in late gestation, small fetuses most impaired by uterine crowding also have impaired erythropoiesis. The gilts were genotyped using genetic markers spaced at regular intervals throughout the swine genome and the average fetal hematocrit and fetal plasma iron values for each maternal gilt was used to determine chromosomal regions influencing these traits. A region on chromosome 12 had a significant effect on plasma iron and the beneficial allele originated with the Meishan founder animals (Vallet *et al.*, 1999d). Further studies of the influence of this region on plasma iron including examination of candidate genes within this region that may be responsible for these effects are underway.

Iron and folate effects on litter size

There are numerous reports in which the effect of exogenous iron and/ or folate on litter size has been determined. However, exogenous iron treatment does not increase litter size (Spruill *et al.*, 1971; Lillie and Frobish, 1978; O'Connor *et al.*, 1989; Guise and Penny, 1990). The effect of folate treatment on litter size is equivocal, some studies indicate an increase in litter size in response to treatment (Matte *et al.*, 1984; Lindemann and Kornegay, 1989; Thaler *et al.*, 1989) while others indicate no effect (Tremblay *et al.*, 1989; Harper *et al.*, 1994). These disappointing results are not unexpected, given that the amount of iron and folate delivered to the conceptus during pregnancy is controlled by the secretion rates of uteroferrin and FBP, respectively. Furthermore, secretion of both of these proteins is refractory to increased availability of their respective ligands (Vallet *et al.*, 1999b). A reliable test of the influence of improved iron and folate delivery to the conceptus during pregnancy requires a method to significantly alter the secretion rates of uteroferrin and FBP by the uterus.

Conclusion

Currently available data indicate that changes in uterine, placental and fetal function may be exploited to increase uterine capacity. Increased uterine length due to genetic selection for this trait, genetic selection or hormonal manipulations that result in reduced placental size and/ or increased placental efficiency or genetic selection, marker assisted selection or other treatment schemes to improve fetal erythropoiesis

during early and late gestation may also benefit uterine capacity. In each case, increased uterine capacity increases the potential for increased litter size. However, in order for increased uterine capacity to be translated into a realized increase in litter size, it must be combined with methods to increase the number of available embryos (e.g., increased ovulation rate or embryo transfer).

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जे.एल. वैलेट। शूकरों में गर्भाशय क्षमता पर भ्रूण रक्ताणु उत्पत्ति एवं अन्य कारकों का प्रभाव।

विलगाव के समय शूकरों के स्वस्थ एवं ज्यादा बच्चे शूकर उत्पादन क्षमता का एक मुख्य विषय है। यह अण्डोत्सर्ग की दर, निषेचन दर, जल्द भ्रूण मृत्यु एवं गर्भाशय क्षमता जैसे विभिन्न कारकों द्वारा प्रभावित होती है। आनुवांशिक चयन के साथ-साथ हार्मोन परिचालन गर्भाशय क्षमता को बढ़ाने तथा प्लैसेन्टा के आकार को कम करने एवं उसकी क्षमता बढ़ाने में सक्षम पाया गया। आनुवांशिक चयन, चिन्हक सहायक चयन या अन्य उपचारों के कारण शुद्ध एवं बाद की गर्भावधि के समय भ्रूण रक्ताणु उत्पत्ति की सहायता से गर्भाशय क्षमता भी विकसित हुयी।