

# Role of placental function in mediating conceptus growth and survival<sup>1,2</sup>

M. E. Wilson<sup>3</sup>

Division of Animal and Veterinary Science, West Virginia University, Morgantown 26506-6108

**ABSTRACT:** Conceptus mortality is a significant factor limiting reproductive efficiency of livestock. In both singlet- (i.e., cattle) and litter- (i.e., pigs and sheep) bearing species, investigations of conceptus mortality have focused on the period immediately preceding and throughout the attachment phase, around the time of maternal recognition of pregnancy. Recently, data have emerged leading to the suggestion that conceptus loss later in gestation is also significant and that variation in placental size and function may play a very important part in determining whether a conceptus survives. In the pig, the number of conceptuses present after the initial period of loss that survive to term appears to be influenced by the total amount of placental mass present, such that litters containing individuals with relatively small placentae have a greater potential for a large litter size when compared with litters containing similar numbers of individuals with relatively large placentae. In ruminants, recent evidence supports the time of placental development and initial vasculari-

zation (between d 28 and 40) as a second period of significant loss, particularly in situations involving manipulation (ovulation synchronization for timed AI in cattle and out-of-season breeding in sheep). In the pig, not only does placental size vary, but efficiency (as measured by the ratio of fetal weight to placental weight) can also vary as much as threefold within a litter, leading to the suggestion that selection for small, very efficient placentae may provide a mechanism for increasing litter size. In ruminants, there are obvious cases where placental growth has been markedly altered (i.e., large offspring syndrome or heat stress) and a subsequent deviation from "normal" placental efficiency occurs. Less information is available on normal variation in placental size and efficiency; however, the timing of the secondary period of loss supports a role for events during placental development and vascularization being critical to survival and potentially contributing to the observed loss.

Key Words: Conceptus Survival, Placental Function, Reproductive Efficiency

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## Introduction

A major limitation to the reproductive efficiency of livestock species is the loss of conceptuses during gestation (Edey, 1969; Short, 1984; Rohrer et al., 1999). Historically, the peri-implantation period has been identified as a period of significant conceptus loss in swine (Corner, 1923; Perry, 1954; Scofield, 1972), cattle (Hammond, 1914; Hanly, 1961), and sheep (Boshier, 1969; Guillomot et al., 1981). The peri-implantation period is characterized by dramatic morphological changes in the

embryo, including elongation, and by the initiation of an intimate attachment between the outer embryonic membrane and the uterine luminal epithelium (Perry and Rowlands, 1962). The dramatic nature of these developmental stages has led to suggestions that losses are a result of asynchronous development between the uterus and embryo, or among embryos within a litter (Dziuk, 1987). Conceptus loss during the peri-implantation period is estimated at 30 to 40% in pigs (reviewed by Pope, 1994) and 20 to 30% in ruminants (reviewed by Zavy, 1994). Recently, evidence has emerged that appreciable conceptus loss occurs during later gestation (Foxcroft, 1997; Wilson et al., 2000; Inskeep, 2001). Although conceptus loss during later gestation does not represent the largest component of total loss, it is significant and negatively impacts reproductive efficiency in livestock species. This review will focus on the potential role that variation in placental function may play in contributing to the variation in conceptus survival observed, and the implication of variations in placental function with regard to growth and survival of the neonate.

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<sup>3</sup>Correspondence: G048 Agricultural Science (phone: 304-293-2406, ext. 4425; fax: 304-293-2232; e-mail: mwilso25@wvu.edu).

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## Conceptus Loss After Attachment

### *Pig*

During the last 30 yr, evidence has accumulated that around d 30 of gestation, the capacity of the uterus becomes limiting. In cases where the number of embryos present during early gestation is increased (either by transfer of additional embryos to an already pregnant female or by superovulation), embryos are lost during the peri-implantation period in proportions similar to those in normal pregnancies (i.e., 30 to 40%), resulting in an increased number of conceptuses present after d 18. However, the additional conceptuses surviving beyond d 18 are lost after d 30 such that similar numbers of conceptuses are present at term as observed for control females (Fenton et al., 1972; Pope et al., 1972; Huang et al., 1987). Additionally, in sows that are unilaterally hysterectomized-ovariectomized, ovarian compensation will result in an ovulation rate similar to that of controls, with only one-half the uterine space available. As with the experimental models that increase the number of embryos in an intact uterus, reducing the amount of uterine space results in a relatively stable proportion of embryos lost prior to d 30, with approximately one-half the normal number of conceptuses surviving to term (Christenson et al., 1987). Several recent investigations employing current commercial sow lines have reported relatively high ovulation rates (i.e., approximately 26; Foxcroft, 1997; Wilson et al., 2000). As with females induced to have large numbers of conceptuses by superovulation or superinduction, these sows exhibit a 30 to 40% conceptus loss by d 25 of gestation ( $16 \pm 1$  viable conceptuses). Uterine capacity then becomes limiting, and an additional 15% of the original number of potential conceptuses are lost ( $12 \pm 1$  viable conceptuses), confirming the notion that uterine capacity becomes limiting sometime after d 30 in animals without experimental intervention (Wilson et al., 2000). More than 10 yr ago, the Meishan breed was imported into the United States to examine the biological underpinnings of its prolificacy (Bazer et al., 1988). Meishan gilts exhibit similar ovulation rates and uterine sizes to occidental breeds used for comparison (i.e., Yorkshire, Large White, and the USDA MARC white composite) while giving birth to three to five more pigs per litter (Christenson, 1993; Galvin et al., 1993; Lee et al., 1995). A component of the increased prolificacy is reduced peri-implantation conceptus mortality (Ford, 1997). In addition to increasing the proportion of conceptuses that survive the peri-implantation period, a greater number of conceptuses are able to survive to term. A major component of this increased prolificacy appears to be the reduced placental size of the Meishan conceptus as compared with the Yorkshire conceptus throughout gestation, allowing more conceptuses to occupy a similar amount of space in utero (Ashworth et al., 1990; Biensen et al., 1998; Wilson et al., 1998). This decreased placental size likely results from

a decreased preimplantation embryonic growth rate, leading to a decreased length of Meishan vs. Yorkshire embryos after elongation, and probably allows more of the embryos surviving to d 30 to colonize the uterus (Ashworth et al., 1990; Ford et al., 1994). Nutrient allocation to a conceptus would be expected to be reduced by the small size of the Meishan placenta; however, when Meishan and Yorkshire littermate conceptuses are cogenated in either a Meishan or Yorkshire uterine environment, the piglets will have similar birth weights (Wilson et al., 1998, 1999). The similarity in piglet weights in the face of marked differences in placental size appears to result from the markedly greater density of blood vessels for nutrient uptake in the Meishan placenta compared with the Yorkshire placenta during the final third of gestation (Biensen et al., 1998).

### *Ruminants*

Current and emerging technologies to increase reproductive efficiency in ruminants include methodologies to control the synchrony and timing of ovulation in cattle to facilitate breeding management and reduce labor cost of estrus detection and the use of progestogen treatments to facilitate normal luteal function, improving pregnancy rates to ram-induced out-of-season breeding in sheep (Inskeep, 2001; Knights et al., 2001). The development and widespread use of transrectal ultrasonography for the diagnosis of ovarian function and pregnancy status very early in gestation (i.e., d 25 of gestation) has allowed investigators to ascertain the pregnancy status of females very early on and to better characterize conceptus loss. Recently, Inskeep (2001) summarized a number of current reports of significant conceptus loss in individuals assigned to timed AI protocols. The described pregnancy loss between approximately d 25 and 40 to 70 of gestation was approximately 15%, but varied widely among groups, ranging from 7.7 to 45.9%. The key observation is that embryos appear to survive the early stages of gestation when gross genetic abnormalities would be expected to result in embryonic loss (Butcher and Fugo, 1967), but they die shortly after the transition from the yolk sac as the source of nutrition to the chorioallantoic placenta, supporting the idea that either abnormalities in the chorioallantoic placenta or an inappropriate transition cause embryo loss. Unfortunately, there is a paucity of experimental data on this period of conceptus loss, and therefore we must rely on educated speculation and hope, in the years to come, to expand the observational data to include experimentation.

## Placentation

The major physiological developmental event that occurs during the early stages of gestation, after attachment, is the initial growth and development of the placenta, referred to as placentation. This very important biological phenomenon begins with the outgrowth from

the embryonic hindgut of the allantois (Patten, 1948). The allantois will grow to fill the chorionic sac, fusing with it to form the chorioallantoic portion of the fetal membranes. Our guiding hypothesis has involved the as yet unsubstantiated notion that the size attained by the chorion is directly proportional to the length the embryo attains during elongation and is limiting to the size of the vascularized chorioallantoic membrane (Wilson and Ford, 2000). The apparent timing of the conceptus loss during the fourth to seventh week of gestation in pigs, sheep, and cattle concurrent with the outgrowth, fusion, and establishment of the chorioallantoic membrane is suggestive of at least a partial role either in all or some subset of embryonic loss. In the pig, as an example of the noninvasive placentation seen in livestock, placental weight increases exponentially between d 20 and 60 of gestation (Pomeroy, 1960; Knight et al., 1977). The weight of the placenta increases steadily throughout the remainder of gestation (Pomeroy, 1960; Knight et al., 1977; Biensen et al., 1998). Several authors have argued that placental weight does not change after 70 d of gestation; however, these authors all ceased measurement of placental weight on or before 105 d of gestation, the time of the initiation of the secondary increase (Knight et al., 1977; Vallet et al., 1996; Klemcke and Christenson, 1997). The surface area of the chorioallantoic membrane increases rapidly from d 35 to 70 (Knight et al., 1977). On d 35, the surface area is approximately 250 cm<sup>2</sup>, whereas by d 70, it is approximately 1,000 cm<sup>2</sup> (Knight et al., 1977; Biensen et al., 1998). By d 60 to 70 of gestation, there exists an interlocking network of fetal and maternal microvilli, furthering the massive exchange surface of the placenta (Friess et al., 1980; Björkman and Dantzer, 1987; Biensen et al., 1998). From d 70 to 100, there is little change in placental surface area (Knight et al., 1977). However, sometime after d 100, there is a marked increase in the surface area of the placenta, reaching approximately 1,500 cm<sup>2</sup> (Biensen et al., 1998), or even doubling in size by d 110 (Wigmore and Strickland, 1985).

In sheep, the allantois first appears on d 14 to 15 of gestation and expands to fill the extraembryonic space, eventually fusing with and vascularizing the chorion, giving rise to the chorioallantoic membrane. The embryo will begin to interact with the uterine luminal epithelium once it has completed elongation via loose attachments, initially in the region of the embryonic disk, but soon spreading to the remainder of the chorionic membrane (Guillomot et al., 1981; King, 1993). This attachment initially occurs throughout the chorioallantoic surface (Guillomot et al., 1981). Between d 16 to 18 of gestation, the portions of the chorioallantoic membrane overlying the caruncles (specialized structures dispersed throughout the uterine lining for nutrient and waste product exchange between the maternal and conceptus compartments) begin to interdigitate with the caruncular epithelium. This initial interaction of the chorioallantoic membrane with the underlying

caruncle begins in the region immediately surrounding the embryonic disk and spreads from there, similar to the case for the initial loose attachment (Perry, 1981).

Further development of the caruncle and the associated chorioallantoic membrane (to be called the cotyledon) will result in the development of a mature placentome (Björkman and Dantzer, 1987). The placentomes will account for the majority of blood flow to the gravid uterus by term (Reynolds and Redmer, 1995). Cotyledons will first develop simple villi that fill the crypts found in the caruncles, forming an initial adherence to the uterine lining. These villi proliferate, forming complex structures coursing throughout the caruncle, which, now activated, will increase in size dramatically during gestation (Stegeman, 1974). Lining the placentomal crypts are large binucleated cells, possibly a fusion product of the caruncular and cotyledonary epithelia or a result of chorionic epithelial cells that have undergone karyokinesis without cytokinesis. In the regions between placentomes, the chorionic epithelium loosely adheres to the endometrial epithelium, except over the uterine glands where areolae (specialized structures for the absorption of uterine glandular secretions) form (Guillomot, 1981).

### Placental Efficiency

Placental efficiency has been described for a number of species as simply the weight of the fetal component of the conceptus divided by the weight of the placental component (Molteni et al., 1978; Kurz et al., 1999). Although this view of placental function does not take into account, or do justice to, the complexity and diversity of mechanisms involved in nutrient (Dantzer, 1982; Battaglia, 1986; Sibley et al., 1997), gas and waste (Carter, 1989) exchange between the conceptus and the maternal system (Davies, 1960; Faber and Thornburg, 1986; Munro, 1986), its simplistic nature allows for significant, repeatable variations in placental function to be described. As mentioned above, one of the striking differences between the Meishan pig and the occidental breeds to which it was compared is the substantial reduction in placental size. Throughout gestation, the Meishan pig exhibits a reduced placental size in conjunction with a reduced embryonic size prior to elongation. Evidence from studies with the pig support the suggestion that the early development of the embryo has long-term impacts on conceptus growth and development (Ford, 1997; Wilson et al., 1998; Wilson and Ford, 2000). Embryos of the Meishan breed exhibit a markedly slower growth rate throughout the preimplantation period, elongate to a shorter length around d 12 of gestation, and have a markedly smaller placenta throughout the remainder of gestation when compared with commercial breeds (Ford, 1997; Wilson et al., 1998). The slower growth rate of the Meishan embryo has been attributed to a dramatically slower proliferation of the cells of the trophoblastic layer and is evident as early as d 6 of gestation, as measured by a

reduced number of trophoblast cells per inner cell mass cell (Rivera et al., 1997). Slower growth continues through d 12 of gestation, as measured by a reduced apparent mitotic rate in the trophoblast (Wilson and Ford, 1997). Slower proliferation of the trophoblast is consistent with the observed smaller placental size as the trophoblast will become the outer layer of the the chorioallantoic membrane. In association with the reduced early embryonic growth rate, the Meishan has a markedly lower uterine luminal content of a number of histotrophic components, including IGF-I (Wilson and Ford, 1997). Additionally, treatment of early d-5 to -6 pig embryos with insulin (an IGF-I receptor agonist) resulted in a increased embryonic diameter following 24 h of culture, consistent with a role for the IGF system in modulating very early embryonic growth (Lewis et al., 1992). In an effort to understand better the role of placental size and function in pigs, a series of experiments was conducted to determine the contributions of both the conceptus and the maternal environment in establishing the size and function of the placenta. Several of these experiments involved cotransfer of Meishan and Yorkshire embryos to a common uterine environment to facilitate direct comparison of littermate Meishan and Yorkshire conceptuses. The pivotal experiment focusing attention on placental function as a key component in conceptus survival involved cotransfer of Meishan and Yorkshire embryos on d 2 of gestation to Yorkshire recipient females, which were then allowed to farrow. At term, Meishan and Yorkshire pigs were born at similar weights, with Meishan pigs attached to placentae approximately two-thirds the size of their Yorkshire littermates. Notably, the Meishan placentae exhibited an apparently greater vascular density throughout the chorioallantoic membrane. This concept of variation in placental vascularity contributing to the variation in placental size and function has a long history, dating back at least to the report of McKenzie and Bogart (1934) on the contribution of the size and "quality" (i.e., color, integrity, etc.) of cotyledons in the placentae of lambs as an indicator of the thrift of the lambs. Recently, Reynolds and Redmer (2001) again affirmed the concept that the appropriate growth and development of the placenta is paramount for the success of gestation. Measures of poor placental function (oxygen delivery to the conceptus), as well as experimental models including carunclectomy and heat stress that establish poor placental function, are evident very early on in gestation, prior to the dramatic exponential increase in fetal weight during the final one-third of gestation, supporting the notion that abnormal placental function leads to abnormal fetal growth.

The longstanding assumption that restriction of placental growth can force an increase in placental efficiency has recently been questioned (Ott et al., 1997). There is no doubt that in cases of massive reductions in placental size as a result of intense uterine crowding, carunclectomy or heat stress can force the placenta to

maximize its efficiency, but there is also evidence that under reasonably normal situations, the efficiency of the placenta has a strong conceptus-directed component. In the pig, studies employing estrogen administration to pregnant Meishan gilts around the time of elongation, in an attempt to increase uterine luminal growth factors and therefore conceptus size, resulted in marked increases in placental size with no reduction in placental efficiency (Wilson and Ford, 2000). Additionally, in Meishan  $\times$  Yorkshire F<sub>1</sub> crosses, the placental efficiency of the crossbred offspring was intermediate to that of the straightbred Meishan and Yorkshire (Biensen et al., 1999). Ott et al. (1997) demonstrated that restricting sheep conceptuses to a single uterine horn decreased placental size without increasing placental efficiency.

### Vascular Development of the Placenta

As early as d 18 of gestation in the pig and sheep and by d 22 to 24 of gestation in the cow, the allantoic membrane fuses with the chorion and the blood vessels of the newly formed chorioallantoic membrane will begin to proliferate (Reynolds and Redmer, 2001). In ruminants, discrete areas of fetal maternal interaction develop between the permanent caruncles dispersed throughout the uterine lining and the ephemeral cotyledons. The cotyledon begins as a focal point of vascular proliferation in the chorioallantoic membrane overlying caruncles. From this point of proliferation, villi will develop and interdigitate with the crypts of the caruncle. In sheep, the density of blood vessels in the cotyledon remains relatively constant through approximately d 80 of gestation, at which point the cotyledonary blood vessel density increases linearly through 140-plus days of gestation (Reynolds and Redmer, 2001). In pigs, the density of blood vessels in the chorioallantoic membrane is relatively constant from d 25 to 45 of gestation and begins increasing linearly between d 45 and 70, continuing this increase until term (Vonnahme et al., 2001). An important component in the function of the placenta during gestation is the development of a sufficient absorptive area, not only in the physical size of the placenta, but also in the number and density of blood vessels for nutrient exchange (Friess et al., 1980; Leiser and Dantzer, 1988; Reynolds and Redmer, 1995). By d 70 of gestation, the placental vasculature accounts for approximately 3.7% of the total volume of the chorioallantoic membrane (Biensen et al., 1998). The density of blood vessels will remain relatively constant during late gestation, occupying 3% of chorioallantoic membrane volume by d 90 and 2.5% of chorioallantoic membrane volume by d 110 (Biensen et al., 1998). Furthermore, Wilson et al. (1998) reported that in farrowed placentae, the vascular volume was approximately 4% of placental volume. Pigs, sheep, and cattle are all described as having a noninvasive placentation, which limits placental function to the rate of both uterine and placental (umbilical) blood flow (Carter and Myatt,

1995). It is worthwhile to note that although placentae in the livestock species are not invasive, they can be very efficient, especially with respect to freely diffusable nutrients, such as oxygen and carbon dioxide, as the distance between maternal and fetal endothelial cell membranes separating fetal and maternal blood is reduced to approximately 2  $\mu\text{m}$  (Friess et al., 1980, 1982).

The extreme nature of vascular growth and proliferation in the placenta, particularly during the later stages of gestation, has made it a tissue of interest for investigators interested in angiogenesis, or the development of new blood vessels from existing ones (Barcroft, 1946; Wallace, 1948; Alexander, 1964). A number of growth factors, several with an affinity for heparin, have been described to promote or enhance one of the three main components of angiogenesis: migration, proliferation, and/or tube formation (Cheung, 1997). One of the most potent of these angiogenic factors is vascular endothelial growth factor (VEGF; Ferrara et al., 1992). The placenta of the sheep produces VEGF and the placental and intercotyledonary tissue are the predominant sites of synthesis in the gravid uterus (Millaway et al., 1989; Reynolds and Redmer, 1995; Reynolds and Redmer, 2001). The density of microvasculature in the cotyledon is relatively constant from d 40 to 80 of gestation, followed by a marked (i.e., 8- to 10-fold), linear increase in cotyledonary vascular density from d 80 until near term in the ewe (Stegeman, 1974). Placental angiogenesis in the last one-half to one-third of gestation is credited for allowing placental (or umbilical) blood flow to continue to increase until term in the face of a lack of increase in placental size or surface area (Reynolds and Redmer, 1995). Observed increases in oxygen extraction from uterine blood in the sheep have been attributed primarily to increases in umbilical blood flow as opposed to any increase in extraction efficiency (Reynolds and Redmer, 1995). An increase in the surface area available for transfer would likely allow for greater increases in placental function during periods of extremely rapid fetal growth. The pig placenta also synthesizes VEGF in the chorionic epithelium very early on in gestation (i.e., d 25; Winther et al., 1999; Vonnahme et al., 2001). This production has been demonstrated at the mRNA level as well as the protein level (Winther et al., 1999; Vonnahme et al., 2001). Vonnahme et al. (2001) demonstrated that the amount of VEGF expressed by the fetal membranes increases during gestation, in a manner very similar to the pattern of vascular development mentioned above. The expression of VEGF by the pig placenta is correlated with placental efficiency, likely as a result of the correlations that exist between VEGF expression and the vascular density of both the placenta and the underlying endometrium (Vonnahme et al., 2001).

### Variation in Placental Efficiency

In the pig, variation in the efficiency of the placenta is marked by as much as threefold variation within

individual litters (Wilson et al., 1999). This tremendous variation led Wilson et al. (1999) to select both boars and gilts that had developed on either large, relatively inefficient placentae or small, relatively efficient placentae. When these boars and gilts were mated within placental efficiency category, the offspring exhibited a pattern of placental efficiency similar to that exhibited by their sire and dam. In addition to the divergent response of the offspring in placental efficiency, those individuals that were selected for a small, efficient placenta gave birth to approximately three more pigs per litter than the individuals selected for large relatively inefficient placentae (Wilson et al., 1999). These results led to the suggestion that uterine capacity is not adequately described by simply the number of offspring carried to term, but better described by the total placental mass a female can carry to term. Defining uterine capacity in such a way allows for variation in litter size as a result of variation in placental efficiency in cases where uterine size is similar. In other words, the number of conceptuses surviving to term is a combination of either physical or physiological uterine size and placental size.

The realized heritability of placental efficiency calculated from the selection experiment employing placental efficiency was 0.37 (Wilson et al., 1999). Recently, Vallet et al. (2001) failed to find an increase in placental efficiency in unilaterally hysterectomized-ovariectomized gilts selected for uterine capacity (simply measured as number of conceptuses) compared with unselected controls. Those authors did observe an increase in placental efficiency in the line selected for ovulation rate. More importantly, in the 422 litters that were collected across all three lines, the heritability of placental efficiency was noteworthy for a reproductive trait ( $0.29 \pm 0.08$ ; Vallet et al., 2001), particularly when compared with reported heritabilities for uterine capacity and litter size (0.09, Young et al., 1996, and 0.16, Hertzler et al., 1940, respectively).

A key component of placental efficiency gleaned from results of studies with pigs throughout gestation, including long before fetal growth markedly outpaces placental growth, is that there is no association between fetal weight and placental efficiency. However, there is a strong negative correlation between placental weight and placental efficiency (Biensen et al., 1999; Wilson et al., 1999, 2000). These associations, or the lack thereof, have been interpreted to suggest that both large and small fetuses can develop on either a small or large placenta, but that generally a small placenta is efficient and a large placenta is inefficient.

### Implications

Conceptus mortality at any stage of gestation reduces reproductive efficiency, either by decreasing litter size in pigs and sheep or by eliminating pregnancy altogether. Placental efficiency appears to influence the number of conceptuses than can survive in a given uter-

ine space and may also influence the survival of a given conceptus in the absence of uterine crowding. A greater understanding of the physiological components associated with conceptus loss should provide the infrastructure necessary to implement strategies to minimize loss.

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