Early nutritional programming and progeny performance: Is reproductive success already set at birth?

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Implications

- Maternal nutrition during gestation influences the development and function of many biological systems in offspring.
- There is evidence to show that both maternal undernutrition and overnutrition during gestation are detrimental to the reproductive development of offspring and that the effects are permanent after birth and visible in adulthood.
- These long-term effects may impair reproductive efficiency in the offspring; hence, nutrition during the entire gestation should be carefully managed to improve fertility.

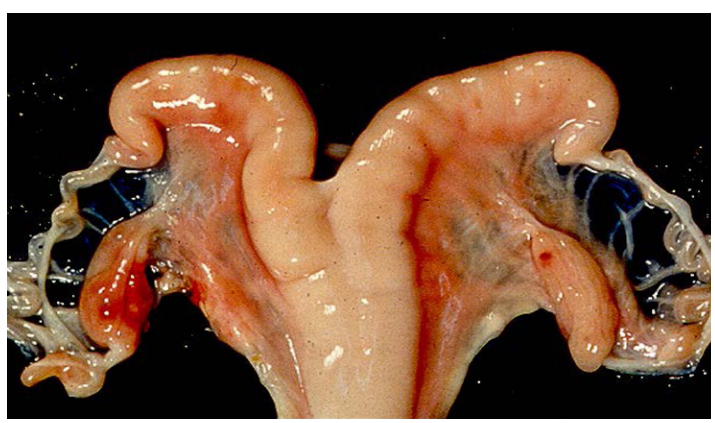
Key words: development, gonads, nutrition, offspring, reproduction

Introduction

Compelling evidence indicates that the environment encountered during fetal life exerts a profound influence on development, physiological function, and risk of disease in adult mammals (Barker, 2007; Langley-Evans and McMullen, 2010). Development is a plastic process, wherein a range of different phenotypes can be expressed from a given genotype. The developing conceptuses respond to conditions in the environment during sensitive periods of cellular proliferation, differentiation, and maturation, resulting in structural and functional changes in cells, tissues, and organ systems. These changes may have short- and/or long-term consequences for health and disease susceptibility. Hence, the term "programming" has been adopted to describe the process whereby a stimulus or an insult at a critical and sensitive period of fetal or perinatal life has permanent effects on the structure, physiology, and metabolism of different organs and systems. Despite many studies investigating the associations between maternal environment during fetal development and the onset of cardiovascular disease, obesity, and diabetes in offspring as adults (McMillen and Robinson, 2005), few studies have investigated the impact of maternal environment on the reproductive potential of offspring. This paper reviews the existing literature on the effects of prenatal and perinatal nutrition on the development and function of the reproductive system in female and male domestic mammals, with particular emphasis on cattle and sheep.

Development of the Reproductive Tract in Female and Male Mammals

In mammals, sex is genetically determined, whereby embryos with an X and a Y chromosome develop as males and those with two X chromosomes develop into females. Nevertheless, during the initial stages of gonadal and genital development, embryos of either sex are morphologically indistinguishable. The urogenital system comprises the gonads, kidneys, urinary, and reproductive tracts and develops from the intermediate mesoderm, formed during gastrulation of the embryo. Before sexual differentiation, the intermediate mesoderm proliferates and generates two pairs of genital ducts: the Wolffian (or mesonephric) and the Müllerian (or paramesonephric) ducts. Sexual differentiation in males is characterized by regression of the Müllerian ducts due to the inhibitory effect of anti-Müllerian hormone (**AMH**), which is secreted by the Sertoli cells of the fetal testis, thus enabling differentiation of the Wolffian ducts into structures of the male reproductive tract, such as the epididymides, vas deferentia, and seminal vesicles. Fetal ovaries do not produce AMH, so the Müllerian ducts that subsequently form adjacent to the Wolffian ducts can persist and differentiate into the oviducts, uterus, cervix, and upper portion of the vagina of the female reproductive tract (Spencer et al., 2012).



Newborn calf overies and uterus.

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Table 1. Timing of reproductive tract development in laboratory rodents, sheep, cattle, and humans. Gestation has been divided into three parts to better emphasize how the development of the reproductive system may be differentially sensitive during selected windows of gestation (Rüsse, 1983; Dupont et al., 2012; Spencer et al., 2012).

	Event (day of gestation/day after birth)			
	Rodents*	**Sheep**	**Cattle**	**Humans**
1st third of gestation	gonadal differentiation (mice 6)	Müllerian ducts formed (24)	germ cells visible (35-36)	male gonadal differentiation (42-49)
	germ cells visible (6.5)	male gonadal differentiation (30)	start of meiosis in female (75-80)	Müllerian ducts fusion (by 56)
		Müllerian ducts fusion (34-55)	primordial follicles visible in female (74-90)	start of meiosis in female (70-98)
		start of meiosis in female (55)		uterine corpus and cervix differentiated (by 84)
2nd third of gestation	germ cells migrate towards the genital ridges (8.5-10.5)	primordial follicles visible in female (75)	primary follicles visible in female (74-140)	primordial follicles visible in female (98-105)
	Wolffian ducts formed (9)	aglandular nodules visible in the uterine endometrium (90)	peak number of germ cells (91-110)	tertiary follicles visible (210-245)
	Müllerian ducts formed (11.5)	primary follicles visible in female (110)	secondary follicles visible (120-210)	
	gonadal differentiation (rat 12.5)			
	start of meiosis in female (mice 13, rat 17)			
	regression of Müllerian ducts in male (13.5)			
3rd third of gestation	fusion of Müllerian ducts (15-16)	endometrial gland development first observed (135)		
		antral follicles visible (135)		
Birth	20 mice, 21 rat	147	282	280
Postnatal life	meiosis of germ cells in male	development of the uterus (up to 26)		Development of endometrial glands (birth-puberty)
	development of the uterus (1-15)			
	primordial follicles (mice 2-5, rat 1-2)			
	primary follicles (mice 2-5, rat 2-3)			
	antral follicles (mice 17, rat 15)			

*Data for rodents are expressed as days post-coitum.

The source and migration of germ cells to the developing gonads is the same in males and females. When primordial gonads begin to differentiate as ovaries or testes, developmental pathways of germ cells diverge, leading to either oogenesis in females or spermatogenesis in males. In a newly specified ovary, germ cells enter into the first phase of meiosis—the special form of cell division unique to germ cells that allows them to produce haploid cells necessary for sexual reproduction. In the fetal ovary, entry into meiosis is seen as the first indication that germ cells have embarked on oogenesis. In a newly specified testis, germ cells enter a period of mitotic quiescence and remain in that state until just before puberty when meiosis commences (Spiller et al., 2012). The timing of development of the reproductive tract differs among species and between sexes; hence, the effect of a nutritional insult may vary depending on the species, the timing at which it occurs, and on fetal gender. Table 1 summarizes the current knowledge for laboratory rodents, sheep, cattle, and humans. Gestation has been divided into three parts to better emphasize how the development of the reproductive system may be differentially sensitive during selected windows of gestation.

Early Maternal Nutrition and Female Offspring Reproductive Development and Function

The effect of a specific environment in utero on the development of the conceptus may be different for female and male offspring. Table 2 summarizes the effects of nutritional manipulation of dams during gestation and lactation on reproductive development in female offspring.

Undernutrition

Farm animals may often be exposed to nutritional deficiencies during gestation and lactation; small ruminants are commonly farmed in areas of marginal land on which nutrient supply may be scarce, and dairy cattle may experience periods of negative energy balance at the start and peak of their lactation, which coincides with the time of insemination and early gestation. Hence, efforts have been aimed at understanding the link between undernutrition and reproductive performance for both research and production scopes.

Sheep. The effect of maternal undernutrition on fetal ovarian development was first investigated in ewes fed either 150% (High Energy) or 50% (Low Energy) of their energy requirements for maintenance (**M**) during early gestation (Borwick et al., 1997). At Day 47 (first third) of gestation, concentrations of oogonia were greater in ovaries of Low compared with High Energy fetuses. At Day 62 (first and start of second third) of gestation, the process of germ cell degeneration was less advanced in Low than High Energy fetal ovaries, as indicated by greater oocyte concentrations and a greater percentage of meiotic cells in Low vs. High Energy ovaries. The authors concluded that undernutrition from the time of mating retards ovarian development in fetal ovaries (Borwick et al., 1997). Nevertheless,

Table 2. Effects of nutritional manipulation of dams during gestation and lactation on reproductive development in female offspring.

	Species	Maternal diet	Period of diet	Effect on the offspring	Reference
1st third of gestation	Sheep	Undernutrition	Mating to early gestation	Delayed fetal ovarian development at 47 and 62 d of gestation	(Borwick et al., 1997)
	Sheep	Undernutrition	Mating to 7 d Mating to15 d	Increased total number of oocytes at 1 and 2 mo old	(Abecia et al., 2014a; Abecia et al., 2014b)
	Sheep	Undernutrition	Mating to 30 d	Increased FSH response to GnRH and small follicles at 10 mo old	(Kotsampasi et al., 2009b)
	Sheep	Undernutrition	31 to 100 d	Decreased number of corpora lutea at 10 mo old	(Kotsampasi et al., 2009b)
	Cattle	Undernutrition	-11 d before insemination – 110 d	Decreased number of follicles, lower AMH and higher FSH concentrations	(Mossa et al., 2013)
	Cattle	Low-high protein	Low protein in first trimester, high protein in second trimester	Smaller largest follicle before puberty, lower densities of primordial, primary and healthy antral follicles as adults	(Sullivan et al., 2009)
2nd and 1st-2nd third of gestation	Sheep	Undernutrition	Various periods mating to 110d	Delayed fetal ovarian development at 110 d gestation	(Rae et al., 2001)
	Sheep	Undernutrition	65 to110 d; 0 to 110 d	Alteration of the expression of genes that regulate apoptosis	(Lea et al., 2006)
	Sheep	Undernutrition	Mating to 95 d	Reduced ovulation rate in adults	(Rae et al., 2002a)
	Sheep	Overnutrition	Mating to 130 d; 4 to 130 d	Fewer follicles in fetuses	(Da Silva et al., 2002, 2003)
3rd third and entire gestation	Cattle	Overnutrition	Third trimester	Higher proportion of heifers calved in the first 21 d of their first calving season	(Cushman et al., 2014)
	Sheep	Undernutrition	47 to 147 d	No difference in ovulation rate in adults	(Gunn et al., 1995)
	Rats	Undernutrition	Entire pregnancy and/or lactation	Advanced pubertal age	(Sloboda et al., 2009)
	Rats	High fat diet	Entire pregnancy and/or lactation	Advanced pubertal age	(Sloboda et al., 2009)
	Pig	Low protein	Entire pregnancy and lactation	Reduced number of antral follicles, increased apoptosis of granulosa cells, higher estradiol concentrations in prepubertal offspring	(Sui et al., 2014)
	Rabbit	High fat	From mating to 27 weeks of age	Higher number of atretic follicles in adults	(Léveillé et al., 2014)

it must be noted that this study compared a Low vs. High Energy diet, but no comparisons were made with a moderate energy diet.

Another trial conducted in ewes reported a delay in fetal ovarian follicular development at Day 110 of gestation as a result of undernutrition (50% M) vs. control diet (100% M) during different periods of pregnancy (Rae et al., 2001), confirming the negative effect of maternal undernutrition on fetal ovarian development. It is noteworthy that ovaries were not examined after birth; hence, a compensatory effect during the remainder of gestation cannot be excluded. Nevertheless, a similar finding was recently reported in prepubertal lambs; maternal nutritional restriction from mating to Day 7 or Day 15 (first third) of gestation resulted in an increase in the total population of oocytes in one- and two-month-old ewe-lambs, respectively (Abecia et al., 2014a, 2014b). We can thus speculate that an increase in the number of oogonia in fetal and prepubertal ovaries exposed to maternal undernutrition may reflect a delay in ovarian development in sheep, but whether this delay has long-term effects on reproductive efficiency after puberty is still unknown.

A study that examined the link between in utero malnutrition and reproductive efficiency in ovine adult offspring reported reduced ovulation rates in adult offspring of undernourished mothers from mating until Day 95 (first and second third) of gestation compared with controls (Rae et al., 2002a). It appears that an increase in the number of oocytes assessed during fetal/prepubertal life may not reflect better reproductive performance after puberty in sheep. Interestingly, a cohort of ewes born to mothers undernourished during the last 100 days (second and third third) of pregnancy did not present an impairment in ovulation rate (Gunn et al., 1995); this is probably due to the fact that undernutrition was imposed during a late window of development. Ten-month-old female lambs undernourished as fetuses during the first month (first and start of second third) of pregnancy had a greater FSH response to GnRH challenge and greater number of small (2 to 3 mm diameter) follicles, whereas when nutritional restriction was imposed from Day 31 to 100 (start of first and second third) of gestation, fewer corpora lutea were observed, indicating a decreased number of ovulations (Kotsampasi et al., 2009b).

Taken together, these studies provide evidence that in utero undernutrition of female ovine fetuses during the first and second third of gestation: 1) causes an increase in the number of oogonia in fetal and prepubertal ovaries, which is likely to reflect a delay in ovarian development; and 2) reduces ovulation rate in adulthood. These results support the hypothesis of a negative effect of undernutrition during early- and mid-pregnancy on female reproductive development in sheep.

Nevertheless, the long-term impact of maternal undernutrition on reproductive efficiency in female offspring in sheep is yet to be completely explored. The slow progress in this area is partly due to the fact that investigating how reproductive success can be programmed in utero/perinatally in domestic animals is challenging because long trials are necessary to allow the offspring to reach puberty and large numbers of animals are required to conduct statistically valid studies.

Finally, the mechanisms whereby undernutrition may alter follicular development *in utero*, and consequently reproductive efficiency after birth, are still unclear. Underfeeding from 65 to 110 d (second third) or from 0 to 110 d (first and second third) of gestation in sheep altered the expression of genes that regulate apoptosis (Lea et al., 2006), but further studies are needed.

Cattle. To identify markers of reproductive potential, a series of experiments conducted in our laboratories identified the number of antral follicles growing during follicular waves (antral follicle count, or **AFC**) and serum AMH concentrations as diagnostic markers for fertility in cattle. Antral follicle count is positively associated with the number of morphologically healthy follicles and oocytes in ovaries (ovarian reserve; Ireland et al., 2008), and cattle with a low AFC have a reduced response to superovulation (Ireland et al., 2007), enhanced FSH secretion (Burns et al., 2005), decreased progesterone production, and reduced endometrial thickness from Day 0 to 6 of the estrous cycle compared with age-matched cattle with high AFC (Jimenez-Krassel et al., 2009; Ireland et al., 2011). In addition, dairy cattle with ≤ 15 ovarian follicles have a reduced reproductive performance compared with cows with greater numbers of follicles (Mossa et al., 2012). Based on these results, we used AFC, AMH, and FSH as markers of the size of the ovarian reserve and reproductive potential to investigate the effect of maternal nutritional restriction during the first trimester of pregnancy on development of female offspring. Female calves born to nutritionally restricted mothers (0.6M for the first 110 d of gestation; first third of gestation) showed lower AFC, lower AMH, and greater FSH concentrations but had similar birth weights, postnatal growth rates (to 95 wk of age), age at puberty, glucose metabolism, and responses to stress compared with offspring from control mothers (1.2M; Mossa et al., 2013). Interestingly, female calves born to nutritionally restricted mothers also had an enlarged aorta and increased arterial blood pressure compared with controls. Whether such phenotypes were both direct consequences of maternal undernutrition or whether compromised vascular function diminished the ovarian reserve and potential fertility is unknown. This study provides evidence for a negative impact of maternal malnutrition on reproductive capacity in adult offspring, but it did not investigate the mechanisms that mediated the effect of maternal undernutrition on ovarian reserve in the offspring. However, an increase in maternal testosterone concentration was detected during dietary restriction in our study.

Another study conducted in cattle provides evidence of the negative effect of early undernutrition on female gonadal development. Heifers born to dams that received a low-protein diet during the first trimester followed by a high-protein diet during the second trimester of pregnancy had smaller follicles and fewer primordial and primary follicles and healthy antral follicles as adults (Sullivan et al., 2009).

Studies investigating maternal undernutrition and offspring reproduction in cattle are limited, probably because of the high costs of such trials due to the length of pregnancy in this species. Findings presented here show that maternal undernutrition during the first third of gestation is inversely associated with several markers of reproductive efficiency in female offspring.

Pigs and rodents. A low-protein diet during gestation and lactation in sows caused a reduction in the number of antral follicles, coupled with an increase in apoptotic granulosa cells and greater circulating estradiol concentrations in prepubertal offspring (Sui et al., 2014). Similarly, in rats, maternal protein restriction decreased numbers of preantral and antral follicles and altered the expression of key genes involved in follicular development and steroidogenesis (Guzmán et al., 2014). The reduction in number of follicles observed in offspring of undernourished mothers after birth appears to be coupled with an alteration in follicular atresia (apoptosis) and steroidogenic activity. Also, in rats, maternal nutrient restriction during pregnancy and/or lactation significantly advanced pubertal age in female offspring (Sloboda et al., 2009).

Hence, the aforementioned negative association between maternal undernutrition and offspring reproductive efficiency observed in sheep and cattle is confirmed in pigs and rats, despite the difference in placentation and in the number of fetuses per pregnancy among these species.

Overnutrition

The study of overnutrition in domestic animals has recently received considerable attention, particularly as a model for humans because obesity has become a global epidemic and diets with high concentrations of fat or sugar are unfortunately common in pregnant women. Yet the number of studies investigating the possible link between maternal overnutrition and fertility in the offspring is limited.

Sheep. A study in sheep reported fewer follicles in the ovaries of female fetuses exposed to high compared with moderate levels of a complete diet from Day 4 to 130 (Da Silva et al., 2002) or from mating to Day 130 of gestation (Da Silva et al., 2003). These studies show that overnutrition, similarly to undernutrition, in early- to mid-gestation may impair the establishment of the ovarian follicular reserve and consequently reproductive potential in female fetuses. Nevertheless, it must be noted that fetal ovaries were examined and further research is needed to determine the long-term effects in ovaries of adult ewes exposed to overnutrition as fetuses.

Cattle. In cattle, a recent study reported that increasing maternal dietary intake during late gestation had no effect on age at puberty or AFC in

Table 3. Effects of nutritional manipulation of dams during gestation and lactation on reproductive development in male offspring.

	Species	Maternal diet	Period of diet	Effect on the offspring	Reference
1st third of gestation	Sheep	Undernutrition	Mating to 50d	Increased expression of mRNA for steroidogenic acute regulatory protein (StAR)	(Rae et al., 2002b)
2nd third of gestation	Sheep	Undernutrition	31 to 110 d	Increased FSH response to GnRH challenge, fewer Sertoli cells at 10 months of age	(Kotsampasi et al., 2009a)
	Cattle	Low protein and low energy diet	1st and 2nd trimester	Increased FSH concentration and increased testicular volume at 5 months of age	(Sullivan et al., 2010)
3rd third of gestation and entire gestation	Sheep	Undernutrition	110 d to lambing	Fewer Sertoli cells and smaller volume of testicular cords at birth	(Alejandro et al., 2002)
	Rat	Low protein	Pregnancy and/or lactation	Reduced LH and testosterone concentrations at 70d of age; reduced fertility rate and sperm count at 270d of age	(Zambrano et al., 2005)
	Rat	Cafeteria diet	Before gestation - weaning; mating-weaning	Impaired sexual behavior, lower FSH, LH, and testosterone concentrations as adults	(Jacobs et al., 2014)
	Rabbit	Hyper-lipidic hyper-cholesterolemic diet	Before gestation - weaning	Lighter testes and epididymis and decreased testosterone concentrations as adults	(Dupont et al., 2014)

female offspring, but an increased proportion of the heifers born to dams fed a high-nutrient diet during the third trimester calved in the first 21 d of their first calving season (Cushman et al., 2014). In turn, AFC was greater in heifers that calved during the first 21 d of their first calving season, thus confirming the usefulness of AFC as a predictor of reproductive capacity (Cushman et al., 2014).

This study provides evidence for a moderate positive effect of a diet with high nutritional levels during the last third of gestation on reproductive efficiency in female offspring. It is noteworthy that the development of the ovarian reserve and age at puberty were not affected by maternal diet, probably because differential diets were imposed during late gestation, when follicles are already formed.

Rabbits and rodents. Sexually mature rabbits exposed to a high-fat diet as fetuses and from birth to 27 wk of age had greater numbers of atretic follicles but similar numbers of primordial, primary, and secondary follicles compared with controls, and their reproductive capacity was not altered (Léveillé et al., 2014). In rats, maternal consumption of a high-fat diet both before and during pregnancy and lactation, or only during pregnancy and lactation, significantly advanced the age of puberty and caused obesity in female offspring (Sloboda et al., 2009).

Taken together, these results provide evidence for a negative effect of overnutrition on fetal ovarian development and age at sexual maturation, but long-term studies are needed to confirm an impairment of reproductive capacity in adulthood.

Early Nutrition and Male Reproductive Development and Function

Undernutrition

Table 3 summarizes the studies reporting effects of nutritional manipulation of dams during gestation and lactation on reproductive development in male offspring.

Sheep. As described earlier, maternal undernutrition during early gestation in sheep altered fetal ovarian development (Rae et al., 2001; Lea et al., 2006), but the same diet during the same period (from mating to Day 110; first and second third of gestation) had no effect on number of Sertoli cells nor on expression of gene products that regulate apoptosis in male offspring (Andrade et al., 2013). Nonetheless, maternal undernutrition applied from mating to Day 50 (first third) of gestation resulted in an increased expression of mRNA for steroidogenic acute regulatory protein (**StAR**) in fetal testes, a protein involved in transport of cholesterol to mitochondria for steroidogenesis, indicating a possible upregulation of fetal testicular steroidogenesis (Rae et al., 2002b). Furthermore, male lambs exposed to undernutrition from 31 to 100 d (end of first and second third) of gestation had an increased FSH response to a GnRH challenge coupled with fewer Sertoli cells at 10 mo of age (Kotsampasi et al., 2009a). Finally, a study in sheep where maternal undernutrition was imposed from 10 wk of gestation until parturition (second and third third of gestation) produced male offspring with fewer Sertoli cells and smaller volumes of testicular cords at birth (Alejandro et al., 2002)..

Rodents. In rats, maternal protein restriction during pregnancy and/or lactation caused a reduction in LH and testosterone concentrations at 70 d of age in male offspring as well as reduced fertility rates and sperm counts at 270 d of age (Zambrano et al., 2005).

Findings in both sheep and rats indicate that undernutrition during pregnancy can reduce testicular development in the newborn, as assessed by a reduction in the number of Sertoli cells.

Overnutrition

In humans, obesity is often caused by excessive consumption of high energy (usually high in sugar and/or fat).

Rodents and rabbit. To investigate the potential effects of such diet on health, researchers conduct experiments on laboratory rodents using the "cafeteria diet," which is composed of highly energetic and palatable human foods (Jacobs et al., 2014). The cafeteria diet includes biscuits, ham, cake, marshmallows, sausages, salami, and soft drinks. The majority of studies focus on metabolic syndrome, obesity, and cardiovascular disease. Yet, in a recent work, adult male offspring of female rats fed a cafeteria diet before gestation (from 21 d of age to mating at 90 d), during gestation and lactation, or from before gestation to lactation showed impaired reproductive behavior, as assessed by a reduction in the percentage of animals displaying intromission behavior and decreases in plasma concentration of testosterone, LH, and FSH (Jacobs et al., 2014). Also, rabbits fed a dietary-induced maternal hyperlipidemia and hypercholesterolemia, administered from 10 wk of age and throughout gestation and lactation, had male offspring with lighter testes and epididymis and decreased testosterone concentrations compared with offspring born to control dams as adults (Dupont et al., 2014).

Cattle. Prepubertal bull calves whose mothers were fed a diet low in protein and energy levels during the first and second trimester of pregnancy had increased prepubertal FSH concentrations and testicular volume compared with calves born to mothers fed a high-protein diet, suggesting a deleterious effect of elevated dietary protein and energy in the first trimester of gestation on reproductive development of their bull calves (Sullivan et al., 2010).

These studies, although limited in number, suggest that male offspring of overnourished mothers may have compromised reproductive potential.

Conclusions

The impact of maternal nutritional imbalance on the development and future function into adulthood of the reproductive systems in both their female and male offspring is relevant. The timing at which mothers are exposed to under- or overnutrition is as significant as the severity of the nutritional imbalance, but many questions remain to be answered. These include whether in utero nutritional effects on reproductive development and function are permanent or reversible. Could heifers exposed during early uterine life to malnutrition, due to, for example, a particularly dry season, be "treated" with a specific compensatory diet later in gestation or early postnatally?

Mechanistic studies are also needed to clarify the paths through which an improper diet affects the growth and function of the reproductive organs and if other factors, such as heat stress during gestation, influence reproductive development and function in offspring.

The real challenge for future studies is to understand how the prenatal environment can be managed to improve reproductive performances of farm animals. As such, more research efforts are needed to understand the extent and the mechanisms whereby maternal nutrition programs reproductive success of their offspring.

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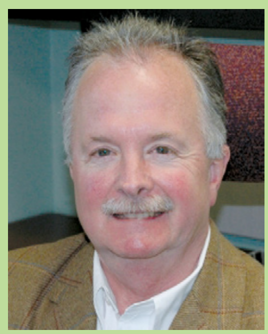

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