Nutritional and lactational effects on follicular development in the pig

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In sows, follicular development is inhibited during lactation, and weaning the piglets allows recruitment and selection of follicles that will undergo preovulatory maturation and ovulate. Lactation inhibits GnRH secretion, and in turn LH secretion, through neuroendocrine stimuli induced by suckling. Pituitary response to GnRH and the sensitivity of the hypothalamo-pituitary unit to oestradiol positive feedback are also reduced. The impact of lactation on the reproductive axis is further complicated by the physiological and metabolic adaptations that are developed for milk production and that depend on nutrient intake, nutrient needs and body reserves. A strongly catabolic state during lactation amplifies the inhibition of LH secretion, thereby inducing a delay of oestrus and ovulation after weaning. Nevertheless, post-weaning ovulation is less delayed nowadays than in the 1970’s or 80’s. Nutritional deficiency has also deleterious effects on embryo survival, which are likely related to alterations in follicular growth and maturation. The physiological mechanisms by which information on the metabolic changes is transmitted to the hypothalamus-pituitary-ovary axis are not fully understood in the sow. Glucose, insulin and leptin are the most likely signals informing the hypothalamus of the metabolic state, yet their roles have not been definitely established. At the ovarian level, folliculogenesis is likely to be altered by the reduction in insulin and IGF-I concentrations induced by nutritional deficiency. More knowledge is needed at the intrafollicular level to better understand nutritional effects on follicular development, and also on oocyte quality and embryo development.

Introduction

In sows, as in numerous mammalian species, parturition is followed by a period of anovulation. Suckling by piglets is the main factor that inhibits the activity of the hypothalamo-pituitary-ovarian axis and the nutritional deficiency related to milk production can amplify the inhibition of the reproductive axis. Lactational and nutritional effects on fertility in sows have been extensively reviewed (Britt et al. 1985, Aherne & Kirkwood 1985, Foxcroft 1992, Einarsson & Rojkittikhun 1993, Quesnel & Prunier 1995). However, nutritional effects on reproductive performance after weaning appear to have changed over the past 20 years towards less delayed ovulation after weaning and deleterious effects are frequently reported on embryo survival (Table 1). Moreover, extensive research has been conducted to better understand the physiological and metabolic mechanisms underlying the nutritional effects on reproduction. The purpose of

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this review is first to update knowledge on the impacts of lactation and nutrition on follicular development, and second to examine potential mechanisms mediating these effects.

Table 1. Influence of feed or protein supply (High or Low) during lactation on the weaning-to-oestrus interval (WOO), ovulation rate (OR) and embryo survival (ES) in sows from first or second parity.

| References                  | Feed supply | Protein supply | Parity | WOO (days) | OR | ES (%) |
|-----------------------------|-------------|----------------|--------|------------|----|--------|
|                             | High Low    | High Low       |        |            |    |        |
| Mullan et al. 1991          | 1           | 8.7 19.2*      | -      | -          |    | -      |
| Zak et al. 1997a             | 1           | 3.7 5.4*       | 19.9   | 15.4*      | 87 | 64*    |
| Zak et al. 1998              | 1           | 4.2 6.3*       | 14.4   | 15.6       | 83 | 72     |
| Van den Brand et al. 2000    | 1           | 5.1 5.4        | 18.2   | 16.9†      | 79 | 68*    |
| Vinsky et al. 2006           | 1           | 5.3 5.4        | 18.3   | 18.2       | 83 | 68*    |
| Kirkwood et al. 1987         | 2           | 4.3 5.8*       | 18.2   | 18.7       | 83 | 72*    |
| Kirkwood et al. 1990         | 2           | 6.0 8.9*       | 17.6   | 17.7       | 83 | 72*    |
| Baidoo et al. 1992           | 2           | 5.9 7.3*       | 16.4   | 17.2       | 81 | 67*    |

* P < 0.05; † P < 0.1.

**Effect of nursing and milk production on follicular development**

*Neuroendocrine and metabolic consequences of nursing and milk production*

In sows, the effects of nursing and milk production cannot be dissociated since lactation is not maintained without suckling by the young. During lactation, stimulation of the teats by piglets and piglet proximity elicit neuroendocrine reflexes that induce the release of neurotransmitters and neuropeptides in the central nervous system of the sow. Neuropeptides include the endogenous opioid peptides (EOP) that have a morphine-like biological activity and include endorphins, enkephalins and dynorphins. These factors, in turn, stimulate the secretion of the pituitary hormones, prolactin, growth hormone (GH), adrenocorticotropic (ACTH), thyroid-stimulating hormone (TSH) and oxytocin (Fig. 1, reviewed by Kraeling & Barb 1990, Estienne & Barb 2005). Thereby, secretion of insulin-like growth factor I (IGF-I), cortisol and thyroid hormones is also stimulated.

These hormones are involved in milk production through different pathways including the regulation of udder development, nutrient uptake and body reserves mobilization (for review, see Père et al. 2008). Oxytocin plays an essential role in milk ejection during each nursing, but could also facilitate the mobilization of body reserves (Valros et al. 2004). Prolactin is essential for the initiation and the maintenance of milk production, and milk protein synthesis (Farmer et al. 2008). Elevated concentrations of GH are thought to favour the preferential drive of glucose and lipids to the mammary gland through the anti-lipogenic action of this hormone. Together with elevated concentrations of IGF-I, they could also minimize mobilization of endogenous proteins and thus spare lean tissue. Cortisol is known to enhance mobilization of energetic substrates from body reserves and thyroid hormones stimulate protein synthesis by the mammary gland, amongst many metabolic actions.

Because of the great use of glucose by the mammary gland, mean blood concentrations of glucose are lower during lactation than during pregnancy. In contrast, concentrations of non-
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Energy balance of sows during lactation may vary from moderately (plain line) to highly negative (interrupted lines). Plasma concentrations of metabolites and metabolic hormones are summarized from various studies (e.g. Rojkittikhun et al. 1992, Schams et al. 1994, Kraetzl et al. 1998, Quesnel et al. 1998a, Govoni et al. 2007).

EOP: endogenous opioid peptides, NEFA: non-esterified fatty acids, ACTH: adrenocorticotropin, TSH: thyroid-stimulating hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone.

Esterified fatty acids (NEFA) are elevated during lactation, which indicates lipid mobilization from adipose tissue. Fat catabolism is induced by the elevated concentrations of GH and also by energy deficiency when sows are not allowed to consume feed ad libitum in early lactation. Elevated concentrations of NEFA are believed to induce the peripheral insulin resistance observed during lactation (Père & Etienne 2007), which is a major physiological adaptation to enhance glucose availability for the mammary gland. Preprandial concentrations of glucose and insulin generally decrease as lactation progresses and milk production increases.

In situations of severe nutritional deficiency, further physiological and metabolic adaptations are developed to maintain a high level of milk production at the expense of maternal body reserves (Fig. 1). Such adaptations are observed in high-yielding multiparous sows and also in most primiparous sows because they have a lower feed intake than multiparous sows but a relatively high milk production. When sows are in a strongly catabolic state induced by feed or protein restriction, IGF-I concentrations are reduced presumably because of the uncoupling of the link between GH and IGF-I secretion (Quesnel et al. 1998a, 2005a, Mejia-Guadarrama et al. 2002). A low level of IGF-I facilitates the mobilization of endogenous protein, which provides amino acids that may be used for gluconeogenesis and milk protein synthesis. Insulin secretion is reduced which allows further mobilization of lipids from adipose tissue. Feed restriction also affects post-prandial concentrations of leptin (Mao et al. 1999), but not pre-prandial concentrations (Prunier et al. 2001, Estienne et al. 2003). Pre-prandial concentrations appear to be highly influenced by sow adiposity (Estienne et al. 2000, 2003, de Rensis et al. 2005).
Effects of suckling on the reproductive axis

During the last month of pregnancy, follicular development and LH secretion are inhibited by progesterone and oestrogens secreted by corpora lutea and the foeto-placental units respectively (reviewed by Quesnel & Prunier 1995). At parturition, circulating concentrations of progesterone and oestrogens fall and LH secretion immediately increases. Two or three days after parturition, LH secretion is inhibited again in suckled sows (de Rensis et al. 1993a). This suckling-related suppression of LH episodic secretion appears to be due to the inhibition of the GnRH pulse generator (Kraeling & Barb 1990). The inhibitory effect is mainly due to EOP during established lactation, whereas its development in early lactation is opioid-independent (de Rensis et al. 1993b, 1998).

In addition to the inhibition of GnRH secretion, the pituitary responsiveness to GnRH is also altered (Quesnel & Prunier 1995). It is low after parturition and increases as lactation progresses. The reduced responsiveness of the pituitary gland can be due the direct action of EOP on the adenohypophysis (Estienne & Barb 2005). It may also be related to LH stores in the pituitary gland, which are depleted just after farrowing and are progressively restored during lactation.

Mean concentrations of plasma LH and number of LH pulses are low during the first two weeks of lactation, and then progressively increase (e.g. Shaw & Foxcroft 1985, Jones & Stahly 1999). This partial resumption of LH secretion can be permitted by the increase in pituitary LH-response to GnRH and (or) by a decrease in suckling intensity in the course of lactation. Indeed, the total time spent nursing was shown to decrease from the 13th day of lactation onwards (Valros et al. 2002). Variations in follicle-stimulating hormone (FSH) are less marked than variations in LH, probably because FSH release is influenced by ovarian secretions during lactation (Quesnel & Prunier 1995). Steroid secretion remains low during lactation and therefore does not influence LH secretion. In contrast, FSH secretion is inhibited by inhibin secreted by growing follicles (Wheaton et al. 1998).

In the ovaries, follicular growth up to 2 mm in diameter does not require gonadotrophic support; growth from 2 to 4 mm requires FSH support and is stimulated by LH, while growth and maturation from 4 mm to the ovulatory size (6-10 mm) requires a high frequency of LH pulses. Consistently, large follicles (≥ 5 mm) can be observed on the ovaries after parturition, and then only small and medium-sized follicles (no larger than 3 mm) are present during the second week of lactation. Afterwards, follicular growth resumes as a consequence of the progressive increase in the frequency of LH pulses. However, follicles generally do not develop beyond 5 mm in diameter during lactation. Beside this general pattern of follicular growth, great variability between sows has been reported in follicular populations before weaning. Using transrectal ultrasonography, Lucy et al. (2001) described sows with relatively inactive ovaries with no follicles larger than 2 mm in diameter and other sows with large follicles (6 mm) present. These authors also suggested the existence of non-ovulatory follicular waves during the week before weaning, consisting of a cohort of follicles that grow to 4-6 mm and then regress. This needs to be further investigated.

During lactation, the positive feedback action of oestradiol on LH release is also impaired. After parturition, the hypothalamo-pituitary unit does not respond to oestrogen positive feedback and its responsiveness is partially recovered in the third and fourth weeks of lactation (for review, see Quesnel & Prunier 1995). However, the amplitude of the LH surge after the injection of a massive dose of oestradiol benzoate remained lower than that observed in similarly treated cyclic or prepubertal gilts. The impaired responsiveness of the sows to oestradiol benzoate could be due to a low pool of LH stores or to the inhibitory effects of EOP on GnRH secretion and pituitary response to GnRH. The dysfunction in the oestradiol-induced positive feedback
Lactational anoestrus in the sow could also be a long-term effect of pregnancy and parturition (Quesnel & Prunier 1995). This hypothesis was based on studies in sows weaned just after parturition. Weaning piglets at birth, instead of 3 to 5 weeks after birth, induces a high incidence of anoestrus and cystic ovaries and delayed ovulation. Anoestrus and cystic ovaries probably result from a lack of an ovulatory LH surge due to reduced hypothalamic response to oestradiol positive feedback. Additionally, the duration of lactation influences the hypothalamic responsiveness to oestradiol in weaned sows; the amplitude of the LH surge induced by exogenous oestradiol is higher after 35 than after 21 of lactation (Edwards & Foxcroft 1983).

Effects of weaning on the reproductive axis

Weaning the piglets removes the inhibition originating from the suckling stimuli, which induces an immediate increase in LH secretion and, although less clear, in FSH secretion. Some follicles are recruited and selected from a pool of medium-sized follicles (2-3 mm) to undergo preovulatory maturation and to ovulate, whereas the other medium-sized follicles become atretic. The preovulatory follicular growth and associated oestradiol production lead to oestrous behaviour and ovulation within 4 to 6 days after weaning, on average.

Variation in the weaning-to-oestrus interval (WOI) is related to the degree of inhibition of LH secretion during lactation (Shaw & Foxcroft 1985). The degree of inhibition of LH secretion during lactation influences follicular development before weaning and the resumption of follicular growth after weaning (Quesnel et al. 1998b). Bracken et al. (2006) reported that the average diameter of follicles at weaning was one factor controlling the WOI duration. The degree of inhibition of LH secretion before weaning also influences LH secretion after weaning (Shaw & Foxcroft 1985, van den Brand et al. 2000).

Does the intensity of suckling modulate the activity of the reproductive axis?

Assessing to what extent the intensity of suckling stimuli can modulate the inhibition of LH secretion is not easy. Most strategies that increase suckling intensity (e.g. increasing litter size, litter weight, age of nursed piglets or nursing frequency) also increase milk yield and can affect sow metabolic state. In multiparous sows, a reduction in LH secretion was reported in association with a longer average nursing duration and not in association with a more catabolic state (Hultén et al. 2002a, b). In an attempt to dissociate suckling and metabolic effects, we compared sows that nursed 13 or 14 piglets and were fed ad libitum to sows that nursed only 7 piglets and were subjected to feed restriction (Quesnel et al. 2007). The sows that nursed a large litter had smaller follicles at weaning than sows with a small litter. Yet, despite a similarly negative energy balance in sows from the two groups, plasma IGF-I concentrations were lower in sows that nursed a large litter. Therefore, we were not fully successful in maintaining an equivalent metabolic state across groups.

Although most sows remain anoestrus throughout lactation, ovulation can occur before weaning. Lactational ovulation is followed by a regular oestrous cycle of 21 days, thereby inducing a delayed oestrus after weaning. Because oestrous behaviour is not usually recorded during lactation, data are scarce on the incidence of lactational ovulation in commercial farms. In a field study based on 7 farms and 492 sows, 3% of sows on average were reported with lactational ovulation, as detected by high concentrations of progesterone at weaning (Auvigne et al. 2006). One may wonder whether strategies implemented at farm level to alleviate side
effects of high prolificacy, such as partial weaning of the heaviest piglets, increase the incidence of lactational ovulation. Moreover, welfare concerns promote the development of housing systems that allow the animals to express their natural behaviour, such as group-housing. Hultén et al. (1995) reported that 28% of the sows housed in groups during weeks 4 and 5 of lactation ovulated before weaning, whereas none of the singly housed sows ovulated during the corresponding period.

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Impact of nutritional deficiency on performance of reproduction

A severe feed restriction associated with body weight loss during lactation delays oestrus after weaning in primiparous sows and to a lesser extent, in second-parity sows (Table 1). In the most recent experiments, the weaning-to-oestrus interval was little influenced by nutritional restriction during lactation (Table 1). This change is probably the consequence of indirect selection on WOI along with genetic selection on prolificacy. Together with the moderately extended WOI, deleterious effects of nutritional restriction are occasionally observed on ovulation rate and consistently on embryo survival (Table 1). Reduction in both ovulation rate and embryonic survival can partly explain the so-called "second litter syndrome" or "second parity dip", i.e. the smaller second litter as compared to the first one. Ultimately, a severe negative impact on embryo survival could explain the reduction in farrowing rate observed after the first weaning. In a field study including nearly 1700 sows, a longer weaning-to-service interval was reported when bodyweight loss during lactation increased above 5% for primiparous sows and above 10% for older sows (Thaker & Bilkei 2005). Yet, all sows returned to oestrus within 7 days after weaning when bodyweight loss did not exceed 15%. Subsequent farrowing rate and litter size were depressed when bodyweight loss exceeded 10%.

Nutritional effects at the hypothalarno-pituitary level

Feed restriction associated with a strongly catabolic state inhibits the episodic secretion of LH during lactation (Mullan et al. 1991, Zak et al. 1997a, 1998, Quesnel et al. 1998b). Since the frequency of LH pulses is tightly controlled by the GnRH pulse generator, the nutritional anoestrus is likely due to the inhibition of GnRH secretion. It is worth noting that a severe restriction in crude protein or digestible energy also delays the post-weaning oestrus through impairment of GnRH and LH secretion during lactation (King & Martin 1989, Koketsu et al. 1996, Jones & Stahly 1999, Yang et al. 2000a). Such restrictions do not occur naturally in herds, but may help understand the mechanisms mediating nutritional effects.

Almond & Dial (1990a, b) suggested that failure to return to oestrus after weaning might also be due, in part, to an increased sensitivity of the hypothalamo-pituitary unit to the negative feedback of oestrogens. In their experiments, however, anoestrus was thought to be due to the seasonal influence on reproduction. In ewes, seasonal anoestrus involves an increased sensitivity of the hypothalamus to oestradiol negative feedback and high feed intake can modify the sensitivity of the hypothalamus to oestradiol (Forcada & Abecia 2006). To our knowledge, a nutritional influence on the sensitivity of the hypothalamo-pituitary unit to oestradiol has not been investigated in the sow.
Metabolic mechanisms mediating nutritional effects at the hypothalamo-pituitary level

The relationships between nutrition and reproduction are most often viewed through energy balance. The influence of energy deficiency on GnRH secretion has been extensively reviewed (e.g. Barb et al. 2001a, Wade & Jones 2004) and general pathways have been proposed. Feed intake modulates the availability of oxidizable metabolic fuels (glucose and fatty acids), which in turn modulate hormonal secretion (insulin, insulin-like growth factors, leptin, etc) by various organs and tissues. In the model proposed by Wade & Jones (2004), available substrates and hormones can modulate the activity of the neurons of GnRH by two ways (Fig. 2). First, the availability in substrates could be detected by the area postrema, located in the hindbrain. This area has a permeable blood-brain barrier and can monitor substrate concentrations in the blood and cerebrospinal fluid. Second, metabolic hormones could modulate substrate availability and neuronal activity directly in the part of the forebrain which contains neurons of GnRH. The first pathway has been inferred from experiments in rodents and sheep where oxidization of substrates was inhibited by chemical inhibitors. In female rats and guinea pig, glucose deprivation induced by an inhibitor of glycolysis interrupts ovulatory cycles, but this effect disappears when the area postrema has previously been destroyed. However, lesions of the area postrema do not block the inhibitory effects of feed deprivation. Therefore, this pathway alone cannot explain the nutritional inhibition of GnRH secretion (Wade & Jones 2004).

Fig. 2 Schematic representation of potential pathways by which nutrient availability could influence GnRH secretion, based on studies in rodents and small ruminants (adapted from Wade & Jones 2004).

Pathway 1. The availability of oxidizable substrates (glucose and fatty acids) is detected by the area postrema (AP) and information is transmitted to the area which contains neurons of GnRH and neurons sensitive to sexual steroids (ventromedial hypothalamus – VMH and preoptic area – POA). Pathway 2. Metabolic substrates modulate hormonal secretion by various organs and tissues, which in turn can modulate the activity of the neurons of GnRH.
In the sow, the metabolic mechanisms underlying the nutritional effect on the reproductive axis are not yet fully understood. In swine as in all monogastric animals, metabolic energy is mainly provided by glucose. In gilts, experimentally-induced glucose deprivation reduced LH pulse frequency (Barb et al. 2001b). Glucose administration to feed-restricted gilts, and the associated rise in circulating concentrations of insulin, induces a rapid increase in LH pulse frequency similar to that observed in response to refeeding (Booth 1990). Conversely, administration of insulin can stimulate LH secretion, as does increased energy supply (Cox et al. 1987). Based on experiments with diabetic pigs, it was suggested that insulin enhances the sensitivity of the hypothalamo-pituitary unit to ovarian positive feedback signal and pituitary responsiveness to GnRH (Cox et al. 1994, Angell et al. 1996). In lactating primiparous sows, increasing mean plasma concentrations of insulin and glucose by feeding a starch-rich diet compared to a fat-rich diet stimulates LH pulses in early lactation (van den Brand et al. 2000). Collectively, these findings support the hypothesis of a positive effect of glucose and insulin on LH secretion in the pig.

Leptin and IGF-I have been identified as putative signals linking metabolic state and neuroendocrine regulation of reproduction, thereby playing a role in puberty attainment in gilts (Barb et al. 2001b, 2008). In the post-partum sow, however, there is no evidence for a causal relationship between IGF-I and LH concentrations. Regarding leptin, Barb et al. (2008) described, in a very comprehensive review, how it is involved in the control of appetite, energy homeostasis and LH secretion. These authors suggested that leptin can link metabolic state and fertility in the gilt and also in the post-partum sow. However, the importance of the role of leptin in the prolonged lactational anoestrus has not been established. De Rensis et al. (2005) reported that fatter sows at farrowing had greater concentrations of leptin, lost more backfat during lactation and had extended WO1 and reduced farrowing rate than thinner sows.

In contrast, it appears from literature on the influence of protein supply (Jones & Stahly 1999, Yang et al. 2000a, Quesnel et al. 2005a) that restriction in protein alone during lactation impairs LH secretion without reducing fat tissue reserves and leptin concentrations. It induces an intense mobilization of endogenous protein and alters amino acids profiles. The reduced concentrations of insulin in protein-restricted sows could play a major role in mediating the inhibitory impact of protein restriction. Besides, as some amino acids are necessary for the synthesis of neurotransmitters involved in the secretion of GnRH, we suggested that a reduction in their availability could participate in the inhibition of GnRH secretion during lactation (Quesnel et al. 2005a, b). This hypothesis needs to be further investigated.

**Physiological and metabolic mechanisms underlying nutritional effects at the ovarian level**

Compared with sows fed ad libitum, primiparous sows fed half the ad libitum feed supply had inhibited secretion of LH, fewer follicles larger than 4 mm at weaning and two days later, and reduced follicular concentrations of IGF-I (Quesnel et al. 1998b). Clowes et al. (2003a, b) reported that protein restriction and the associated loss in maternal body protein impair folliculogenesis after weaning, as shown by reduced number and diameter of follicles and reduced follicular content of IGF-I and oestradiol at weaning. Additionally, follicular fluid recovered from sows subjected to feed or protein restriction showed a poor ability to support oocyte maturation in vitro (Zak et al. 1997b, Yang et al. 2000b, Clowes et al. 2003b). Nutritional deficiency during lactation can therefore alter both follicular growth and maturation after weaning.

Follicular development is controlled by interactions between gonadotrophins, metabolic hormones (such as insulin and IGF-I) and intra-ovarian growth factors (including IGFs; for review, see Webb et al. 2007). Notably, it is well established that insulin and IGF-I increase ovarian
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response to gonadotrophins and stimulate steroidogenesis (Adashi et al. 1992). Therefore, it is likely that reduced concentrations of insulin and IGF-I in feed-restricted sows impair ovarian responsiveness to the gonadotrophic stimulation at weaning and alter subsequent follicular development and ovulation rate. To our knowledge, however, there is no data on the nutritional effects on intra-follicular IGF binding proteins, which modulate IGF-I bioavailability. Whether elevated concentrations of GH during lactation may inhibit follicular development remains unknown, since both stimulatory and inhibitory actions of GH were reported on follicular steroidogenesis in vitro and in vivo.

The potential role of leptin at the ovarian level is not clear. Leptin has been shown to attenuate in vitro oestradiol secretion by follicular cells stimulated by insulin, IGF-I or gonadotrophins in several species, including the pig. Given that negative energy balance is associated with both low leptin and impaired folliculogenesis, it seems unlikely that direct effects of leptin at the ovarian level are involved in the impairment of folliculogenesis. Nevertheless, Gregoraszczuk et al. (2007) reported recently an in vitro synergistic action of leptin with IGF-I on oestradiol secretion by pig follicles. Another candidate, adiponectin, has been recently proposed as a mediator of the nutritional effects at the ovarian level. Adiponectin is an adipocyte-derived hormone that plays an important role in lipid metabolism and glucose homeostasis. It was shown to induce preovulatory changes in porcine granulosa cells in vitro (Ledoux et al. 2006) and to enhance the stimulatory action of IGF-I on steroidogenesis in the rat (Chabrolle et al. 2007). Low plasma concentrations of adiponectin have been associated with reproductive disorders related to obesity, including the polycystic ovarian syndrome (Campos et al. 2008). Whether adiponectin secretion is influenced by excessive fat loss associated with severe energy deficiency is not known.

Feed or protein restriction has also been shown to impair oocyte quality, i.e. its ability to be fertilized and develop into an embryo (Zak et al. 1997b, Yang et al. 2000b). Like follicular development, oocyte quality is influenced by a complex hormonal background, including gonadotrophins, IGF-I and steroids (Webb et al. 2007, Hunter & Paradis, 2009). Extensive research has been conducted on nutritional effects on oocytes and embryos, mainly from cyclic gilts. Findings support the concept that alteration of these hormones may underlie the impact of nutritional inadequacy on oocyte quality. In turn, follicular and oocyte quality influences embryonic development and survival. To our knowledge, however, little is known on nutritional effects on intrafollicular characteristics (IGF system, glucose utilization, insulin and leptin receptors...). The metabolic cues supporting the impact of the metabolic state on oocyte maturation and embryo survival are beyond the scope of the present review.

Interestingly, detrimental consequences on ovulation rate or embryo survival were mostly reported together with a relatively short WOI duration. Sow energy balance becomes positive as soon as piglets are weaned. However, metabolic state cannot be determined only as a function of energy balance, as previously shown (Quesnel et al. 2007, Zak et al. 2008). Consistently, IGF-I concentration requires several days after weaning before it is restored to normal (van den Brand et al. 2001, Mejia-Guadarrama et al. 2002). Presumably, these sows that ovulate soon after weaning have not fully recovered from their lactational catabolic state. Evidence for this hypothesis was provided by experiments where post-weaning insemination was delayed. Extending artificially the weaning-to-oestrus interval by treatment with altrenogest, an analogue of progesterone, or inseminating sows at the second oestrus after weaning ("skip-a-heat") resulted in increased ovulation rate and/or higher embryo survival (Martinet-Botté et al. 1994, Clowes et al. 1994, Wellen et al. 2007, Patterson et al. 2008). Moreover, delaying post-weaning ovulation increases the preovulatory size of the largest follicles by nearly 1 mm (Wellen et al. 2007, van Leeuwen et al. 2009). Whether a smaller ovulatory size reflects a reduced maturity and lower follicle and oocyte quality remains to be determined.
Role of body reserves

There is evidence that maternal body reserves interact with feed or nutrient intake during lactation to influence post-weaning performance of reproduction.

We demonstrated that greater body weight at farrowing (and at weaning) played a protective role against the detrimental impact of a protein restriction in primiparous sows (Quesnel et al. 2005b). The protein restriction impaired the return to oestrus and reduced ovulation rate after weaning in sows weighing 180 kg at farrowing but not in sows weighing 240 kg. Consistently, sows weighing 165 kg at farrowing had less developed ovaries at weaning than sows weighing 190 kg, despite a similar protein deficiency during lactation (Clowes et al. 2003a). Large body reserves could partly prevent negative nutritional effects by providing energetic substrates and thereby attenuating metabolic and physiological perturbations.

Conclusions

Lactation inhibits LH secretion by inhibiting GnRH secretion and reducing pituitary response to GnRH. As lactation progresses, LH secretion increases, which allows resumption of folliculogenesis. The nutritional deficiency associated with mobilization of body reserves constitutes an additional inhibitory factor, which affects LH secretion and follicular maturation during lactation and after weaning. The lactational and nutritional effects at the different levels of the reproductive axis are likely to influence the ovarian response to lactation management strategies (e.g. short lactation duration, split-weaning, interrupted suckling), as reviewed by Soede et al. (2009). The metabolic mechanisms that affect folliculogenesis are not fully understood (Fig. 3). Glucose, insulin and leptin are the most likely signals at the hypothalamic level, yet their roles have not been definitely established. At the ovarian level, folliculogenesis is likely to be altered by the reduction in insulin and IGF-I concentrations induced by the nutritional deficiency. However, more knowledge on nutritional effects on intrafollicular characteristics, such as IGF, glucose/insulin and leptin systems, could provide a better understanding on nutritional effects on follicular development, oocyte quality and embryo development.

![Fig. 3 Putative sites of action for metabolic substrates and metabolic hormones in the reproductive axis in the sow submitted to feed restriction.](image)

Interrupted line: the potential stimulatory effect is reduced in situation of feed restriction. Dotted line: poor evidence of the effect in swine.
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