Endocrine dynamics associated with follicle development in pigs: a review

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Abstract

A significant increase in growth of follicles that are selected for ovulation seems to occur on days 14-17 of the estrous cycle. In pigs there is a continuous growth of follicles without appearance of dominant follicles or follicle waves during the estrous cycle. There is a general consensus that a decrease of FSH during the follicular phase is accompanied with the selection of ovulatory follicles and changing from FSH to LH dependence. Development of preovulatory follicles is prevented during lactation mainly due to the inhibition of LH secretion. FSH is not inhibited during lactation and temporary increase in FSH is associated with wave-like follicular growth. Weaning of piglets normally results in increased secretion of LH, which is characterized by a high pulse frequency and low pulse amplitude. The duration of weaning-to-estrus interval is associated with plasma changes in gonadotropins, steroids, inhibin, leptin, IGF-I and insulin. Evidence for a positive role of short elevations in cortisol on LH secretion and ovarian function are accumulating but further studies are still needed to elucidate this issue. The aim of this review was to summarize our current knowledge of endocrinological changes in relation to follicular development during estrous cycle, lactation and after weaning in pigs.

Keywords: cortisol, follicular growth, gonadotropins, inhibin, metabolic hormones, pigs.

Introduction

During the last two decades, several technical improvements allowed to study endocrine alterations related to follicular development in the pig. Before introduction of transrectal ultrasonography (Soede *et al*., 1992) the only possible ways to study follicular development in pigs were either to inspect and make morphological examinations of the ovaries after slaughter (Holness and Hunter, 1975; Kunavongkrit *et al*., 1982; Dalin, 1987), or to carry out laborious laparoscopic examinations (Holness and Hunter, 1975; Kunavongkrit *et al*., 1983). The available data collected by Varley and Foxcroft (1990) suggested that, in lactating sows, follicular growth would be accelerated by major increases in episodic LH secretion in the presence of adequate plasma concentrations of FSH. The reduction of the inhibitory effect of suckling and/or lactation may stimulate hormonal changes leading to growth of follicles. Frequent transrectal ultrasonography makes it possible to correlate follicle growth with plasma levels of gonadotropins, steroids, inhibin as well as key metabolic hormones. Thus, a better understanding can be achieved about the mechanisms leading to shortening of the weaning-to-estrus interval by split-weaning (Zak *et al*., 2007), to induction of lactational estrus by intermittent suckling (Gerritsen *et al*., 2008) or about the effects of feeding on the release of hormones (Kauffold *et al*., 2008). The importance of weaning-to-estrus interval for the sow fertility has been described by Tummaruk *et al*. (2000). Data from 6989 sows clearly indicated that subsequent litter sizes decreased by about one piglet when this interval increased from 4 to 10 days. The longer weaning-to-estrus interval had also negative effect on the subsequent farrowing rate (Tummaruk *et al*., 2000). The aim of this review was to summarize our current knowledge of endocrinological changes related to follicular development during estrous cycle, lactation and after weaning in pigs.

Gonadotropins, inhibin and estradiol during estrous cycle

A significant increase in the growth of follicles selected for ovulation seems to occur on days 14-17 of the estrous cycle (Foxcroft and Hunter, 1985; Ryan *et al*., 1994; Cox, 1997). Ryan *et al*. (1994) reported that the number of follicles increased from approximately 20 at day 4 to 45 at days 16-17 of the estrous cycle. The percentage of large follicles greater than 5 mm increased from 6% at days 16-19 to 12% at day 20. These authors could not find any evidence of follicular waves in sows, which is in agreement with findings of other studies (Dalin, 1987; Dalin *et al*., 1995; Guthrie and Cooper, 1996; Evans, 2003), who concluded that, in pigs, during the estrous cycle and particularly during the luteal phase, there is continuous growth of follicles without appearance of dominant follicles or follicle waves. According to Knox (2005), in gilts, the number of large follicles greater than 6.9 mm started to increase on day 15 of the estrous cycle, reaching a maximum during the first day of estrus (day 0). During the same period, the number of small and medium-sized follicles were decreasing (Knox, 2005).

Hasegawa *et al*. (1988) reported that concentrations of serum inhibin revealed two small peaks during the luteal phase and a large plateau peak, which reached its maximum four days before ovulation

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during the estrous cycle in sows. This maximum concentration of inhibin coincided with the lowest concentration of FSH. This study clearly showed a negative correlation between inhibin and FSH particularly during the period from -4 days before ovulation to 3 days after ovulation. Hunter *et al*. (1996) found no difference in mean FSH concentrations between Meishan and Large White sows during the periovulatory period but higher plasma inhibin concentrations in highly ovulating Meishan sows. In addition, plasma concentrations of FSH during the estrous cycle in sows from a line selected on an index that emphasized increased ovulation rate and in sows from a control line were not related to ovulation rate (Mariscal *et al*., 1998). Knox *et al*. (2003) found that the concentration of FSH started decreasing from around day 15 of the normal estrous cycle i.e., with 19-21 days interestrous intervals. Gilts expressing high ovulation rate had a significantly higher plasma concentration of FSH than gilts with low ovulation rate during the ovulatory period and the luteal phase of estrous cycle. Interestingly, concentrations of the inhibin α-subunit were higher in highly ovulating gilts than in gilts with low ovulation rate during the entire estrous cycle (Knox *et al*., 2003). The impact of inhibin on the ovulatory rate can be studied by using an active immunization against inhibin. King *et al*. (1993) who immunized gilts against inhibin observed a 39% increase in the ovulation rate (17.8 vs. 12.8). Serum concentrations of FSH in the immunized gilts were higher than in the control gilts before the ovulatory surge of LH, but were lower after the surge. On the other hand, an increase in the ovulation rate did not influence the secretion of estradiol, LH and progesterone.

Picton *et al*. (1999) investigated the effect of the infusion of purified FSH on follicle development in hypogonadotrophic GnRH agonist-treated gilts. Infusion with FSH increased the maximum follicle diameter and tended to increase the number of follicles greater than or equal to 6 mm of diameter per animal. However, the production of estradiol and testosterone in individual follicles was impaired. Thus, evidence is accumulating that FSH alone is not able to stimulate the growth of large follicles or even estradiol secretion in gilts (Guthrie, 2005). The other way to increase ovulation rate in gilts is to feed animals with a modified diet. Ferguson *et al*. (2003) reported that feeding the high volume diet of 3.5 kg per day for 19 days resulted in a significantly higher number of LH pulses per 8 h during both luteal and follicular phase of estrous cycle compared with gilts fed maintenance diet of 1.35 kg. In fact, there were more ovulatory follicles and higher proportion of oocytes reaching metaphase II in gilts in the experimental group than in those in the control group. That fact was associated with lower plasma concentrations of progesterone and estradiol and higher follicular concentrations of estradiol. FSH concentrations were not affected by difference in nutritional regimes but were significantly lower, as expected, in both groups during the follicular than the luteal phase. This decrease of FSH during follicular phase is accompanied by the selection of ovulatory follicles (Guthrie, 2005).

Further research is needed to elucidate the importance of observed FSH surges for follicle recruitment or maintenance during the estrous cycle in relation to inhibin. Because measurements of circulating inhibins relied on antibodies raised against α-subunit or their synthetic fragments it is likely to be confounded by inability of the applied methods to discriminate between non-bioactive free α-subunit and dimeric inhibins. Medan *et al*. (2007) concluded that the distinct patterns of inhibin A and inhibin B secretion indicate the unique regulation of inhibin A and inhibin B by gonadotropins and the stage of follicular development. Thus, for a precise investigation of the endocrine and paracrine role of inhibin in pigs it would be of importance to develop methods for measuring inhibin A and B.

Gonadotropins, inhibin and estradiol during lactation, before and after weaning

Trout *et al*. (1992) concluded that there is an inverse relationship between concentrations of FSH and inhibin in sows after weaning but not during the preovulatory surge of FSH. These authors found a positive correlation between concentration of inhibin and estradiol in ovarian venous plasma as well as between inhibin and the number of follicles larger than 4 mm in size, collected from sows after weaning. In this interesting study (Trout *et al*., 1992) it was also recorded a significant difference in concentrations of inhibin between estrous and anestrous sows after weaning. Sows showing estrus at day 5 after weaning had continuous increase of inhibin until the day of estrus whereas the concentration of inhibin in anestrous sows stopped to increase and were significantly lower 3-5 days after weaning. In addition, it was observed that estrous sows had higher concentrations of FSH at weaning than anestrous sows. The concentrations of FSH decreased in both groups after weaning reaching nadir at day 2.5. The post-weaning decrease of FSH diminished or prevented by treatment of sows with antiserum against inhibin had little if any effect on subsequent reproductive performance (Wheaton *et al*., 1998).

The effect of lactation length on follicular development in weaned sows was studied by Knox and Zas (2001) who used a transrectal 7.5-MHZ linear transducer. These authors found that average size of the three largest follicles during the first day of estrus after weaning was independent of the length of lactation and varied between 8.0 and 8.5 mm. The sows that failed to express estrus until day 6 after weaning had ovaries with follicles less than 6.0 mm in size. Lucy *et al*. (2001) reported that sows ovulating at day 5 after weaning initiated follicular growth immediately after

136

Anim. Reprod., v.6, n.1, p.135-143, Jan./Mar. 2009

weaning and had follicles larger than 6 mm around day 2. In contrast, sows ovulating at day 9 after weaning had follicles greater than 6 mm around day 6. According to Lucy *et al*. (2001), follicular waves occur in sows before weaning because the peaks of follicular activity are preceded by an increase in concentrations of FSH that might stimulate a new wave of follicular development. These authors observed that the follicular development was associated with an increase in plasma concentrations of estradiol and a decrease in plasma concentrations of FSH. An opposite situation was recorded during the regression of follicles with decreasing concentrations of estradiol and increasing concentrations of FSH (Lucy *et al*., 2001). Willis *et al*. (2003) measured FSH and estradiol in conventionally weaned primiparous sows i.e. on day 24 of lactation. They found that mean plasma concentrations of FSH increased approximately 0.5-fold within 4-5 hours after weaning and stayed at this level until late afternoon of the same day. From midnight of the day after weaning there was a continuous decrease in concentrations of FSH with parallel increase in concentrations of estradiol, which could indicate follicular development according to Lucy *et al*. (2001). Further evidence that the development of an ovarian follicle pool before weaning is one factor controlling the length of weaning-to-estrus interval was presented by Bracken *et al*. (2006). These authors reported that a delay of estrus and ovulation in weaned sows is due to decreased follicular size and number of follicles during late lactation in sows treated with charcoal-treated follicular fluid before weaning (day 20). Serum concentrations of FSH in the treated sows were higher during the first 3 days after weaning than in the control animals. However, there was no effect of treatment on concentrations of estradiol.

The effect of different feeding levels during days 10 and 20 of lactation on secretion pattern of FSH and follicular development recorded by transcutaneous ultrasonography in primiparous sows was studied by Kauffold *et al*. (2008). These authors observed no increase of follicle diameter associated with decreasing concentrations of FSH between day 10 and 20 of lactation in sows fed 70% of ad libitum level. In sows fed ad libitum, mean size of follicles increased from 1.4 to 3.3 mm during the same time and was related with an increase in concentrations of FSH, which were significantly higher than for sows fed at lower levels. Mejia-Guadarrama *et al*. (2002) observed that primiparous sows fed diet with restriction of protein and lysine content (0.5%) throughout 28 days of lactation had higher concentrations of FSH on the day after weaning and lower ovulation rate in comparison with sows fed a normal diet with 1.08% lysine, although no difference in weaning-to-estrus interval was observed. An association between lysine intake and concentration of FSH in weaned sows was also found by Yang *et al*. (2008). However, their results are opposite to Mejia-

Guadarrama *et al*. (2002) because sows fed a low lysine diet during late gestation (0.6%) and 24 days of lactation (1.0% lysine) had lower mean FSH concentration on the weaning day and a longer weaning-to-estrus interval than sows fed high lysine diet i.e., 0.8% lysine during gestation and 1.3% lysine during lactation. A plausible reason for the different results between these two publications is a difference in the definition of low and high lysine content in the diet. Furthermore, Yang *et al*. (2008) reported that multiparous sows having higher concentrations of FSH on the weaning day returned to estrus earlier when compared to primiparous sows.

In early weaned primiparous sows i.e. day 14, concentrations of FSH were higher whereas concentrations of estradiol were lower on the day after weaning than in conventionally weaned sows i.e. day 24 (Willis *et al*., 2003), and with a tendency for a longer weaning-to-estrus interval. These authors concluded that the endocrine data from early weaned sows are characteristic of animals with limited follicular development and incomplete recovery of the hypothalamic-pituitary-ovarian axis. Even though the GnRH infusion during days 12-14 of lactation stimulated follicular growth followed by a decrease in concentrations of FSH and an increase in concentrations of estradiol, these changes were reversed within 24 h after the end of infusion (Bracken *et al*., 2007). These authors concluded that the hypothesis regarding increasing the number of large follicles around the time of weaning would advance follicular development after weaning is still to be proved. Furthermore, their data suggest that the follicular cohort that develops in response to stimulation by LH after weaning depends on the continuous support from the pituitary.

Plasma concentrations of LH and number of LH pulses are low during early lactation and gradually increase from about days 4 to 14 (Stevenson *et al*., 1981; Shaw and Foxcroft, 1985; De Rensis *et al*., 1993). Measurements of LH in blood samples collected continuously, using an automatic collection system, revealed that average and basal concentrations of LH and the number of LH pulses significantly increased between day 10 and 20 of lactation in primiparous sows (Rojkittikhun *et al*., 1993). The response of LH during lactation to different doses of GnRH is significant. However, some authors did not observe any difference in the response during different stage of lactation (Stevenson *et al*., 1981; De Rensis *et al*., 1991; Sesti and Britt, 1994) while others found either higher or tendency to higher response of LH during 3-4 weeks than during 1-2 weeks of lactation (Bevers *et al*., 1981; Rojanasthien *et al*., 1987). It is also well established that naloxone, an opioid antagonist, increases LH secretion during lactation (Barb *et al*., 1986; Armstrong *et al*., 1988; Okrasa and Kalamarz, 1996; De Rensis *et al*., 1998). The other factor influencing secretion of LH during lactation is the duration of nursing in multiparous

sows (Hultén *et al*., 2002). Thus, mean and basal concentrations of LH were significantly higher on day 14 and 21 of lactation in sows with average suckling duration of 168 min per 24 h than in sows with average suckling duration of 236 min per 24 h. However, there was no difference in number of LH pulses and peaks expressed per 6 h. Reduction of the suckling stimulus during lactation achieved either by an intermittent suckling regime (Langendijk *et al*., 2007; Gerritsen *et al*., 2008) or by split-weaning (Zak *et al*., 2007) affects LH secretion characteristics and follicular growth. When sows were prevented from suckling their litter during 12 hours per day, the frequency of LH pulses increased and LH amplitude decreased (Langendijk *et al*., 2007). Sows with higher amplitude of LH pulses in the first non-suckling period had smaller follicles on the third day of intermittent suckling. In general, follicle diameter increased when concentrations of estradiol increased with time but a significant correlation between these two parameters was recorded only during the second day of intermittent suckling (Langendijk *et al*., 2007). Sows subjected to intermittent suckling are similar to conventionally weaned sows in timing of onset of estrus, early follicular growth and ovulation rates with exception of the LH surge that is lower (Gerritsen *et al*., 2008). Zak *et al*. (2007) reported that a 3-day period of split-weaning resulted in higher number of follicles equal or higher than 3 mm at weaning and in a shorter weaning-to-estrus interval in primiparous sows compared to sows conventionally weaned at day 21. Mean concentrations of LH in split-weaning sows increased 10 h after commencing of treatment and approached similar level to that in conventionally weaned sows by the day of final weaning.

The endocrine status of estrous and anestrous primiparous sows after weaning also revealed different pattern of basal concentrations of LH, number of LH pulses and peaks per 6 h (Tsuma *et al*., 1995). There was a significant increase of all these parameters for LH in estrous but not in anestrous sows between day -1 and day 2 after weaning. The increase of estradiol concentrations from the day of weaning to day 2 after weaning was also seen only in estrous sows. In agreement with that, there was a significant negative association between maximum, mean and minimum LH concentrations around weaning and weaning-to-estrus interval (Mao *et al*., 1999). Furthermore, Quesnel *et al*. (2005) reported that mean and basal LH concentrations increased from day -1 before weaning to day 1 after weaning in primiparous sows that returned into estrus within 8 days but not in sows with delayed estrus. There are few papers supporting suggestion that LH secretion during lactation is probably an important factor for follicular development and length of weaning-to-estrus interval in primiparous sows (Jones and Stahly, 1999; van den Brand *et al*., 2000; Willis *et al*., 2003; Yang *et al*., 2008).

The question could be raised whether development of ultrasonographic examinations to monitor the individual growth of follicles in pigs would be helpful in a better understanding the significance of follicular waves before weaning in relation to weaning-to-estrus interval.

Are changes in leptin, insulin and IGF-I related to follicular growth?

In two very recent published reviews by Barb *et al*. (2008) and Lucy (2008) effects of leptin, IGF-I and insulin on reproductive axis in pigs were discussed thoroughly. Even though there is room for interesting data to be included in the present review. For example, van den Brand *et al*. (2001) reported that concentrations of IGF-I were positively related with LH pulse frequency on day of weaning as well as with the height of the preovulatory LH peak. This concurs with an association between an improved oocyte quality and higher concentrations of leptin, IGF-I and insulin during estrous cycle in gilts fed a high maintenance diet than in the control gilts (Ferguson *et al*., 2003). Even though plasma concentrations of leptin on day 21 of lactation were not associated with weaning-to-estrus interval in primiparous sows, it was concluded that leptin's role in reproduction is merely permissive (De Rensis *et al*., 2005). It also appears that sows' metabolic status was improved by split-weaning and their concentrations of IGF-I were elevated before and after final weaning (Zak *et al*., 2007). These authors concluded that the positive effects of increased LH secretion on follicular development and weaning-to-estrus interval in spilt-weaned sows will be facilitated at the ovarian level by improvement in metabolic status. In response to weaning, concentrations of insulin increased significantly in primiparous sows with an average weaning-to-estrus interval of 5.6 days (Rojkittikhun *et al*., 1991a, b). In contrast, Paterson and Pearce (1994) reported that concentrations of insulin increased between day -1 before weaning and day 1 after weaning in primiparous sow returning to estrus 32 days after weaning. These authors did not observe any significant changes in insulin in response to weaning in primiparous sows returning to estrus earlier than 14 days after weaning. On the other hand, higher concentrations of insulin, at the day of weaning, in sows fed high lysine diet during lactation were associated with shorter weaning-to-estrus interval in these sows compared with sows fed low lysine diet (Yang *et al*., 2008). Furthermore, data from that study suggest that, at weaning, the pulse frequency of LH was affected by lactating diet and that the basal LH concentration was higher in multiparous sows. There is no doubt that feed intake and energy balance during lactation may alter key metabolic hormones, which in turn affect gonadotropin action at the level of ovary (Barb *et al*., 2008, Lucy, 2008). However, there is a need for more endocrine data based on specific assays for porcine leptin, IGF-1 and even insulin.

Cortisol before ovulation

It is well established that the hypothalamus-pituitary-adrenal axis is activated by stressful stimuli and is responsible for production of cortisol by the adrenal cortex. Sustained elevations of cortisol achieved either by cortisol or ACTH injections during more than 10 days blocked the pre-ovulatory surge of LH and ovulation in gilts (Barb *et al*., 1982; Turner *et al*., 1999). ACTH injections given in a pulsatile manner for 48 h during pro-estrus resulted in 3 to 4-fold increase of cortisol concentrations followed by a prolongation of estrous cycle and a disturbed follicular development (Einarsson *et al*., 2007). High plasma concentrations of cortisol also achieved after administration of ACTH during estrus were associated with high concentrations of inhibin α (Madej *et al*., 2005; Brandt *et al*., 2007b), high concentrations of LH (Brandt *et al*., 2007b) and tendencies to earlier and shorter LH peaks (Brandt *et al*., 2007a) before ovulation in the treated sows than in the control animals. Thus, it was interesting to find out that the highest concentration of cortisol occurred 28 hours before the second ovulation after weaning in the control sows (Fig. 1, adapted from Brandt *et al*., 2007a). This highest concentration of cortisol was concomitant with the last high concentration of LH (Fig. 2, adapted from Brandt *et al*., 2007a). Pearson's correlation coefficients calculated for hormone concentrations in the same sows revealed a positive correlation between cortisol and LH ($r = 0.41$, $P \leq 0.05$) as well as a negative correlation between cortisol and estradiol ($r = -0.48$, $P \leq 0.01$) during time -34 and -28 hours before ovulation. A positive correlation between cortisol and LH found in our study resembles a relevance of transiently elevated cortisol to enhance LH secretion in sows during intermittent suckling with a total separation of piglets for 12 h per day (Langendijk *et al*., 2007). Taken together it would be interesting to investigate the relevance of the cortisol elevation observed on the day of weaning in sows that resumed estrous activity, which did not happen in anestrous sows (Tsuma *et al*., 1995). The findings of Schoonmaker and Erickson (1983) indicate that glucocorticoids might stimulate granulosa cell differentiation. Acute elevations in plasma cortisol concentration may be involved in mediating changes in pituitary responsiveness and the secretion of LH in the peripubertal gilt (Pearce *et al*., 1988). Recently, Sunak *et al*. (2007) suggested that cortisol has a local role in porcine follicle development and even cystic ovarian disease. Thus, elevated concentrations of cortisol seen before ovulation in Swedish Landrace x Swedish Yorkshire sows (Fig. 1) and in Meishan sows during estrus (Wise *et al*., 2001) might have a positive effect on ovarian function. The hypothesis concerning a positive role of cortisol in physiological processes of reproduction is even possibly supported by (Norrby *et al*., 2007) who reported that naturally mated sows had higher short-lasting elevation of cortisol than sows after artificial insemination. In addition, this greater increase of cortisol in naturally mated sows was not accompanied by any elevation of 15-keto-13,14-dihydro-PGF$_{2\alpha}$, the main metabolite of prostaglandin F$_{2\alpha}$, which is seen in inseminated sows (Norrby *et al*., 2007). Whether an increase of cortisol associated with an inhibition of PGF$_{2\alpha}$ is a result of the well-known anti-inflammatory effects of glucocorticoids (Sapolsky *et al*., 2000) remains to be elucidated. In bovine ovulatory follicles, however, there was a clear two-fold increase in the local concentration of cortisol between 24 h before and at the peak of LH surge (Acosta *et al*., 2005). This increase in the local concentration of cortisol might prevent excess inflammatory reactions associated with ovulation and possibly is an integral part of the regulatory mechanism in ovarian physiology (Acosta *et al*., 2005; Hillier, 2007).
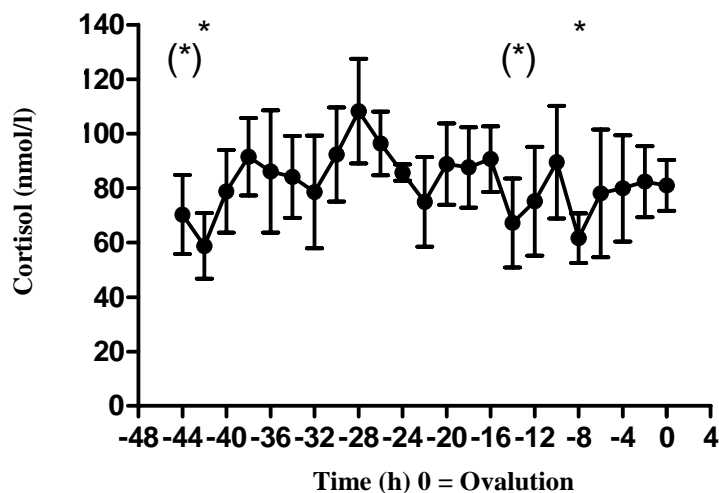

Figure 1. Plasma concentrations of cortisol in the control sows before the second ovulation after weaning (Adapted from Brandt *et al*., 2007a). Note: *$P \leq 0.05$ and $^{(*)}P \leq 0.01$, respectively, vs. value at -28 h.
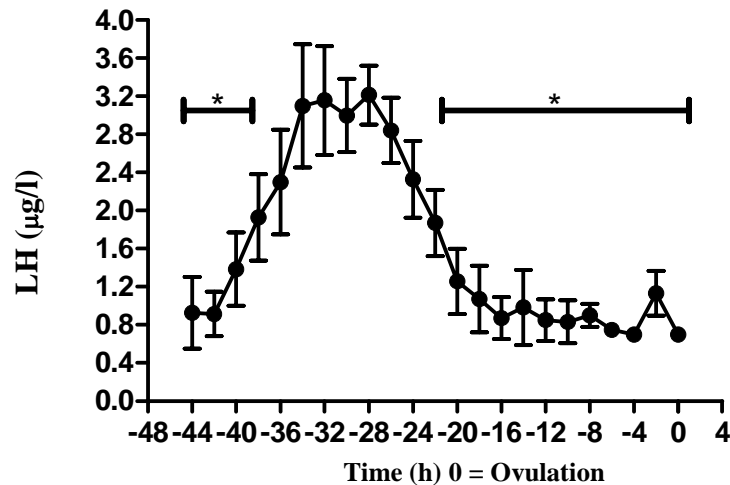
Figure 2. Plasma concentrations of LH in the control sows before the second ovulation after weaning (Adapted from Brandt *et al*., 2007a). Note: *P ≤ 0.05 vs. value at -28 h.

Conclusion

Even though there is a vast literature concerning plasma changes of FSH during estrous cycle, lactation and after weaning in pigs we need more data about the relationship between FSH and inhibin on follicle recruitment and maintenance. To our knowledge, until now, data concerning plasma changes of inhibin A and B in female pigs are not available. At weaning, a sufficient pulse frequency together with the availability of follicles responding to LH are required for follicular growth, which leads to short weaning-to-estrus intervals. The question could be raised whether specific assay for porcine leptin and an assay using monoclonal antibody against porcine insulin would be helpful to clarify the impact of these hormones at different feeding strategies on FSH and LH secretion during lactation and after weaning. Evidence for a positive role of short elevations in cortisol on LH secretion and ovarian function are accumulating but further studies are still needed to elucidate this issue.

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140

Anim. Reprod., v.6, n.1, p.135-143, Jan./Mar. 2009

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Anim. Reprod., v.6, n.1, p.135-143, Jan./Mar. 2009

141

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