Animal 18 (2024) 101339

Contents lists available at ScienceDirect

Animal
The international journal of animal biosciences

Lactation affects postweaning metabolic profiles, but not follicle size in multiparous sows

Q. Yu [a], K.J. Teerds [a], J. Keijer [a], N.M. Soede [b,*]

[a] Human and Animal Physiology, Department of Animal Sciences, Wageningen University, De Elst 1, 6708WD Wageningen, the Netherlands
[b] Adaptation Physiology Group, Department of Animal Sciences, Wageningen University, De Elst 1, 6708WD Wageningen, the Netherlands

ARTICLE INFO

Article history:
Received 18 April 2024
Revised 9 September 2024
Accepted 13 September 2024
Available online 19 September 2024

Keywords:
Follicular development
Growth differentiation factor 15
IGF1
Negative energy balance
Pig

ABSTRACT

Young sows mobilise body reserves to support milk production during lactation, resulting in a negative energy balance (**NEB**). This NEB affects the development of follicles and oocytes that give rise to the next litter. Decreased IGF1 levels due to a NEB are thought to play a role in this process. As this has hardly been studied in multiparous sows, the current study focused on relations between lactation BW loss (%), metabolic hormones, and follicle development in multiparous sows at Day 0 and Day 4 after weaning. A total of 31 sows of parity 4.7 ± 2.5 were killed at either Day 0 or Day 4 after weaning. Average BW loss during lactation was 3.3 ± 4.5%, while average backfat loss was 4.1 ± 0.3 mm. The metabolic profile confirmed the metabolic impact of lactation as both non-esterified fatty acid (**NEFA**), and creatinine levels were higher at Day 0 than that at Day 4. Conversely, serum levels of IGF1 and growth differentiation factor 15 levels were lower on Day 0 than on Day 4. A higher BW loss (%) was related to higher NEFA levels on Day 0, but not on Day 4. IGF1 concentrations in serum and follicle fluid were similar at Day 0 and Day 4 and were not related to follicle size on these days. In conclusion, although lactation affected postweaning metabolic profiles in these multiparous sows, follicle size was not related to these profiles, probably due to the relatively mild BW loss of these sows. IGF1 concentrations were less affected by lactation and did not seem to limit follicle development, as it does in sows experiencing high weight loss.

Implications

In primiparous sows, the lactation period results in a severe negative energy balance, which strongly impacts the development of the follicles and even the next litter. This study investigated if the less severe negative energy balance in multiparous sows also impacts subsequent follicular development. Lactation induced a mild body condition loss and impacted the metabolic blood profile, but did not affect follicle size. Follicle size was not related to body condition loss or to the metabolic profile. Insulin-like growth factor1 levels in follicular fluid were not affected by lactation and therefore cannot serve as a marker for follicle development in multiparous sows.

Introduction

It is generally acknowledged that the metabolic state of a female has a profound influence on reproductive performance in domestic animals, especially pigs (reviewed by Costermans et al., 2022). Especially young sows enter a major negative energy balance (**NEB**) during week 3 to week 4 of the lactation period, due to the high energy requirements for milk production (Gessner et al., 2015). When the energy demand exceeds dietary energy intake, the sows' body reserves, consisting of adipose tissue and muscle proteins, are catabolised and mobilised to supply nutrients for milk production.

It is well documented that these lactation BW losses may impact fertility in primiparous sows (Lucia et al., 2000; Thaker and Bilkei, 2005). Quesnel et al. (1985, 1998) found that a high BW loss in primiparous sows results in a lower average follicle size after weaning. Zak et al. (1997) observed that a higher BW loss in the last week of lactation results in a lower percentage of matured oocytes after *in vitro* maturation. Our previous study confirms these observations: in primiparous sows experiencing a high BW loss during lactation (19.6 ± 1.4% compared to this study) (Hoving et al., 2011; Thaker and Bilkei, 2005), the average size of the 15 largest follicles was significantly reduced, while cumulus–oocyte complexes showed less expansion after 22 h *in vitro* maturation (Costermans et al., 2020a). Generally, a lactation weight loss of more than 10–12% of the initial weight at farrowing is found to affect subsequent reproductive performance (Thaker and Bilkei,

* Corresponding author.
E-mail address: nicoline.soede@wur.nl (N.M. Soede).

https://doi.org/10.1016/j.animal.2024.101339

2005; Schenkel et al., 2010). Primiparous sows lose relatively more BW during lactation than multiparous sows, mostly due to a lower feed intake capacity in the young sows (Eissen et al., 2000). Multiparous sows usually have more body reserves, a higher feed intake capacity, and hardly experience such a high lactation weight loss. The information available about the relation between the metabolic profile and postweaning follicle development in multiparous sows is, however, limited.

The consequences of BW losses on follicle development are mediated by metabolic hormones (Heo et al., 2008). One such hormone is the growth regulatory factor IGF1 (Ford and Howard, 1992; Quesnel et al., 2007). The main site of IGF1 production is the liver, from where, upon its release, it may stimulate follicular development indirectly via affecting gonadotropin release (Van den Brand et al., 2001; Whitley et al., 1995) or directly at the ovarian level (Liu et al., 2000). In first and second parity sows, Han et al. (2020) found that postweaning plasma IGF1 levels are positively associated with follicle diameter. In line with these observations, Costermans et al. (2020a) reported that primiparous sows with the highest percentage of healthy cumulus–oocyte complexes at day 2 after weaning, lose less weight during lactation and have higher plasma IGF1 levels. These observations are further strengthened by Edwards et al. (1996) who observed that under *in vitro* conditions, follicle fluid IGF1 levels increase with follicle size in healthy follicles, while the levels are reduced in atretic follicles. Feed restriction in primiparous sows resulting in a major lactation weight loss, leads to a clearly reduced average follicular size at day 2 postweaning as compared to sows that are fully fed (Costermans et al., 2020a). This study further reports that follicular diameter and follicular fluid IGF1 concentration are correlated. We, therefore, hypothesise that a lactational NEB influences follicular development via modulating circulating and intraovarian IGF1 concentrations.

Growth differentiation factor 15 (**GDF15**), a transforming growth factor-β superfamily member, is closely associated with energy homeostasis (Wang et al., 2021). Several studies report the presence of GDF15 in human follicular fluid (e.g., Souček et al., 2018). We assume that GDF15 may, like IGF1, be associated with follicular development in sows experiencing a lactational NEB.

The aim of the current study is therefore to investigate whether multiparous sows experience lactation BW loss and its possible consequences on parameters for energy mobilisation (creatinine, non-esterified fatty acid (**NEFA**)), and serum and follicle IGF1 and GDF15 levels at Day 0 and Day 4 after weaning, and to determine whether these are associated with follicle size. Preliminary results of these experiments have been published in abstract from Yu et al., (2023ab).

Material and methods

Animals

In this study, we used 31 multiparous Great Yorkshire × Dutch Landrace sows (parity 4.7 ± 2.5; range: 2–10) divided over two batches. Two weeks before farrowing, sows were transported from a commercial farm to the Wageningen University animal facility CARUS. One week prior to parturition, sows were transferred to the farrowing and lactation unit. During farrowing and lactation, sows were exposed to 16 h of light, a room temperature between 18 and 22 °C, and fed a commercial lactation diet (8.66 MJ NE (Megajoules of Net Energy/kg, 148 g/kg CP, 7.7 g/kg SID (standardised ileal digestible) lysine; AgruniekRijnvallei, Wageningen, The Netherlands) at 0800 and 1600 h, in a step-up protocol, reaching 6.5 kg/day at day 12 of lactation. Sows were weaned after 26.9 ± 1.8 days of lactation and killed at the animal facility by electrical stunning and exsanguination at either the day of weaning (Day 0, n = 15) at ca. 1430 h or 4 days later (Day 4, n = 16) at 1030 h. Day groups consisted of sows with similar average parity, lactational BW loss (%), backfat (**BF**) loss (mm), and litter weight at weaning (see Supplementary Table S1). Sows that were killed at Day 4 remained in their lactation pen after weaning and received 2.5 kg of lactation diet daily.

BW, backfat thickness and blood sampling

All sows were weighed approximately 1 week before parturition and immediately after weaning. BW loss was calculated by subtracting BW at weaning from the estimated BW at parturition according to Bergsma et al. (2009). BF was measured at P2, i.e. 6 cm from the backbone at the position of the last rib bone, both on the right and left side of the sow, by ultrasonography (Aquilla, Esaote, Genova, Italy) approximately 1 week before parturition and immediately after weaning as described by Hoving et al. (2011). BF loss was calculated by subtracting BF thickness at weaning from BF thickness at 1 week before parturition.

During exsanguination, blood was collected in serum clot activator tubes (Greiner Bio-One, Monroe, NC, USA). The tubes were kept on ice for 1 h before centrifuging at 3 000 × g for 10 min at 4 °C. After that, the supernatant was aspirated, transferred to labelled Eppendorf tubes, and stored at −80 °C until further analyses.

Follicle size and follicular fluid collection

The left and right ovaries were separately placed on millimeter scale paper and photographed from three different angles. The diameter of the 15 largest visible follicles on the photographs of each ovary's surface was measured by ImageJ (version 1.51f, National Institutes of Health, USA), divided into three tertiles, and classified as Large (1–5), Medium (6–10) or Small (11–15). Follicular fluid was aspirated from the 15 largest follicles on the right ovary using a 21Gx 5/8 needle (0.8 × 16 mm) and 1−ml syringe (TerumoTMAganiTM, Amsterdam, The Netherlands). The follicular fluid samples were pooled per 5 follicles, i.e. Large (1–5), Medium (6–10) and Small (11–15) follicles. The samples were centrifuged at 1 600 × g at 4 °C for 10 min, and the supernatant was collected. The total follicular fluid volume of each pool was assessed by reverse pipetting. Follicular fluid was subsequently stored at −80 °C until ELISA analysis.

Blood serum and follicular fluid measurements

Serum and follicular fluid IGF1 concentrations were measured using a commercial porcine IGF1 ELISA Kit (#SEA050Po, cloud-Clone Corp, Wuhan, China). Serum GDF15 concentrations were measured using a commercial porcine GDF15 ELISA Kit (#SEC034Hu, BlueGene Biotech, Shanghai, China), and serum leptin concentrations were measured using a commercial porcine Leptin ELISA Kit (#CSB-E06815p, Cusabio Life Science Inc., Wuhan, China). All assay procedures were performed according to the manufacturer's instructions. For the measurement of serum creatinine levels, an enzymatic calorimetric test was used (#117599910021, Creatinine PAP FS, DiaSys Diagnostic Systems GmbH, Holzheim, Germany). A calorimetric detection method was also used to measure serum NEFA concentrations (#993-35191, NEFA-HR (2) kit; Wako Chemicals, Neuss, Germany) according to the manufacturer's instructions with slight modifications. Briefly, 5 µl of serum was added to a 96-well plate, followed by the addition of 100 µl of reagent 1, after which the plate was incubated for 10 min at 37 °C. Subsequently, 50 µl of reagent 2 was added to the plate,

followed by another incubation step of 10 min at 37 °C. Detailed information is shown in Supplementary Material S1.

Statistical analyses

ANOVA was applied to continuous data by using the mixed model procedure of SAS 9.1 (SAS Inst. Inc., Cary, NC, USA). Distributions of the means and residuals were examined to verify model assumptions of normality and homogeneity of variance. Statistical models to evaluate influences on metabolic and follicular parameters, always included sampling day (Day 0, n = 15 and Day 4, n = 16), either parity (2–10) or BW loss (%) (−3.98–11.2%) or BF loss (mm) (0.5–12) (Supplementary Table S1) or metabolic or follicular parameter as a covariate, and their interaction with Day. Batch (n = 2) was set as a random factor. Interactions between day and parity or BW loss (%) were omitted from the model if not significant. The detailed information on the analyses is shown in Supplementary Material S1. Data are presented as means ± SEM. The *P*-value < 0.05 is considered statistically significant, while the *P*-value < 0.10 is considered to show a trend.

Results

Body condition and litter weight

During lactation, the average BW loss was 8.4 ± 11.3 kg (3.3 ± 4.5% of BW) and BF loss was 4.1 ± 0.3 mm. As expected, BW loss (%) was related to BF loss (mm) (β_t = -0.33; *P*-value = 0.022) and also to the number of piglets at weaning (β_t = 0.21; *P*-value = 0.027). Parity was related to BW at weaning (β_t = 7.7; *P*-value = 0.0001), and parity was not related to BF at weaning (*P*-value = 0.85), but it was related to BF loss during lactation (mm) (βt = −0.33; *P*-value = 0.046) (Supplementary Table S2).

Serum metabolic parameters

Interactions between Day and Parity never affected serum concentrations of NEFA, leptin, creatinine, IGF1, and GDF15, and neither did the interaction between Day and BF loss. However, for NEFA levels, an interaction was found between Day and BW loss (%) (Table 1).

Both serum NEFA and creatinine levels were significantly higher at Day 0 than that at Day 4. In contrast, serum IGF1 and GDF15 levels were significantly lower at Day 0 than that at Day 4 (Table 2).

Creatinine and serum IGF1 concentrations were significantly affected by parity (Table 1, Fig. 1A and 1B). BW loss was only significantly related to NEFA levels at Day 0 (Fig. 1C), and not related to the other hormones, like GDF15 (Table 1). BF loss was significantly related to NEFA levels (Fig. 1D).

Follicular parameters

The total number of follicles visible on the ovarian surface significantly decreased from Day 0 to 4 postweaning (Table 2). The combined average follicle size of the 15 largest follicles of the two ovaries, the 2 × 15 largest follicles being the presumptive ovulatory follicle pool, increased, not surprisingly, significantly from Day 0 to 4 (Table 2). Unexpectedly, follicular fluid IGF1 levels did not differ between Day 0 and Day 4, neither for the Large tertile (1–5) nor for the Small tertile (11–15) of the largest 15 follicles (Table 2). Follicular fluid IGF1 levels in the Large follicles were not related to IGF1 levels in the Small follicles (*P*-value = 0.14; Fig. 2A). Furthermore, there was no relation between follicular fluid levels and follicular size.

Parity as a covariate was positively related to the average follicle size of the 15 largest follicles of each ovary (Table 1, Fig. 2B). In addition, parity was negatively related to follicular fluid IGF1 levels in Large follicles (Table 1; Fig. 2C) and Small follicles (Table 1; Fig. 2D). No significant relations were found between follicular fluid IGF1 levels and follicle size in either Large or Small follicles, neither for Day 0 nor Day 4, respectively. BW loss (%) tended to be positively related to follicular fluid IGF1 levels in the Large tertile (1–5) of the largest 15 follicles on the ovary and BF loss tended to be negatively related to the size of the Smallest tertile (11–15) of the 15 largest follicles on the ovary (Table 1).

None of the metabolic parameters (e.g. NEFA, creatinine, GDF15, serum IGF1, and leptin) were related to follicle size parameters at either Day 0 or Day 4 (data not shown).

Table 1
Effects[1] of sow parity, BW loss (%) and BF loss (%) during lactation on metabolic parameters and follicular parameters in sows.

	Parity		BW loss (%)		BF loss (mm)	
Parameters	βt	*P*-value	βt	*P*-value	βt	*P*-value
Serum metabolic parameters						
NEFA (nmol/l)	5.85	0.72	[5]	[5]	39.68	0.03
Leptin (ng/ml)	0.45	0.64	−0.30	0.56	−0.11	0.92
Creatinine (mg/dl)	0.11	0.002	−0.014	0.51	−0.019	0.67
IGF1 (ng/ml)	−9.63	0.01	3.14	0.15	4.18	0.39
GDF15 (ng/ml)	0.04	0.57	−0.041	0.28	−0.0042	0.96
Follicular parameters						
Number of visible follicles	1.11	0.29	0.39	0.49	0.59	0.63
Follicle size (mm)[2]	0.14	0.01	−0.019	0.54	−0.10	0.12
Large[3]	0.15	0.02	−0.013	0.72	−0.13	0.096
Medium[3]	0.17	0.004	−0.022	0.51	−0.097	0.17
Small[3]	0.11	0.03	−0.021	0.48	−0.083	0.18
Follicle fluid IGF1 (ng/ml)						
Large[4]	−13.0	0.003	4.2	0.097	2.3	0.77
Small[4]	−11.0	0.010	3.7	0.12	12	0.08

Abbreviations: BF = backfat, βt = regression coefficient for Day 0 and Day 4 together, NEFAs = non-esterified fatty acids, GDF15 = growth differentiation factor 15.
[1] After correction for Day effect (Day 0 vs Day 4). Interactions between Day and Parity, BW loss (%) and BF loss (mm) were never significant, except for the effect of BW loss (%) on NEFA levels.
[2] Average follicle size of 30 follicles, being the 15 largest follicles on both the Left and the Right ovary.
[3] Average follicle size of the 10 Large, 10 Medium and 10 Small follicles of the 30 largest follicles.
[4] Measured in the 5 Large and 5 Small follicles of the 15 largest follicles on one ovary.
[5] β_0 at Day 0 is 47.5 and *P*-value < 0.0001; β_4 at Day 4 is −0.86, *P*-value = 0.92.

Table 2
Effects of Day after weaning (Day 0, n = 15; Day 4, n = 16) on metabolic parameters and follicular parameters in sows.

Parameters	Day after weaning		*P*-value
	Day 0	Day 4	
Serum metabolic parameters			
NEFA (nmol/l)	0.79 ± 0.08	0.24 ± 0.02	<0.0001
Leptin (ng/ml)	3.5 ± 0.3	6.1 ± 0.2	0.50
Creatinine (mg/dl)	2.3 ± 0.1	1.7 ± 0.1	0.003
IGF1 (ng/ml)	242 ± 12	300 ± 11	0.01
GDF15 (ng/ml)	1.4 ± 0.2	2.1 ± 0.3	0.03
Follicular parameters			
Number of visible follicles	62 ± 5	41 ± 2	0.0005
Follicle size[1], mm (mm)[1]	2.6 ± 0.21	4.9 ± 0.18	<0.0001
Large[2]	3.4 ± 0.24	6.2 ± 0.20	<0.0001
Medium[2]	2.6 ± 0.22	4.7 ± 0.18	<0.0001
Small[2]	2.0 ± 0.17	3.6 ± 0.18	<0.0001
Follicle fluid IGF1 (ng/ml)			
Large[3]	263 ± 17	308 ± 14	0.13
Small[3]	254 ± 16	290 ± 23	0.40

All values are presented as mean ± SEM.
Abbreviations: NEFAs = non-esterified fatty acids, GDF15 = Growth differentiation factor 15.
Interactions between Day and Parity were never significant.
[1] Average follicle size of 30 follicles, being the 15 largest follicles on both the Left and the Right ovary.
[2] Average follicle size of the 10 Large, 10 Medium and 10 Small follicles of the 30 largest follicles.
[3] Measured in the 5 Large and 5 Small follicles of the 15 largest follicles on one ovary.

Discussion

In the underlying study, we investigated in multiparous sows if and how postweaning follicle development was affected by BW loss, BF loss, and parity, with a special focus on the relation with the levels of the metabolic hormones IGF1 and GDF15.

The sows in our study lost 3.3 ± 4.5% of their BW and 4.1 ± 0.3 mm of BF during lactation. Not surprisingly, at Day 0 postweaning, this BW loss is strongly associated with an increase in NEFA levels, a product of BF mobilisation/triglyceride degradation (Arner, 2003; Mosnier et al., 2010). BW loss was not associated with the other serum biomarkers for metabolic status, including creatinine which is a biomarker for muscle catabolism (Belstra et al., 1998). One reason for the absence of a significant correlation between creatinine levels and BW loss might be that the BW loss in these multiparous sows mainly consists of fat tissue loss and to a lesser extent protein (muscle) loss. In a previous study, using multiparous sows, Costermans et al. (2019) found that sows that lost more BF during lactation had lower loin muscle losses. Unfortunately, we were unable to measure loin muscle depth in the current study. Nevertheless, our observations suggest that multiparous sows do enter a lactational NEB and preferably use BF for energy mobilisation to compensate for this energy deficit.

The serum levels of the biomarkers for metabolic status, NEFA, creatinine, IGF1, and GDF15 showed significant differences between Day 0, the day of weaning, and Day 4 postweaning. A postweaning drop in plasma NEFA concentrations has been previously reported by Hoving et al. (2012) in primiparous sows. In addition, in our study, serum IGF1 levels are significantly higher on Day 4 after weaning compared to Day 0, extending the results of Wientjes et al. (2013) in multiparous sows and Han et al. (2020) in parity 1 + 2 sows, who both reported a steady increase in plasma IGF1 concentration postweaning. IGF1 is a nutrient-regulated growth factor that mediates many of the anabolic effects of growth hormone (Caregaro et al., 2001). In line with these observations, serum GDF15 levels were significantly lower on Day 0, compared to Day 4 after weaning. Although serum GDF15 levels are not related to BW losses and BF losses, they are negatively correlated to NEFA levels (β_0 = −0.0017, *P*-value = 0.027; data not shown). This correlation suggests that sow's fatty acid metabolism is influenced during lactation (Wang et al., 2021). Souček and colleagues (2018) showed that there is evidence for local

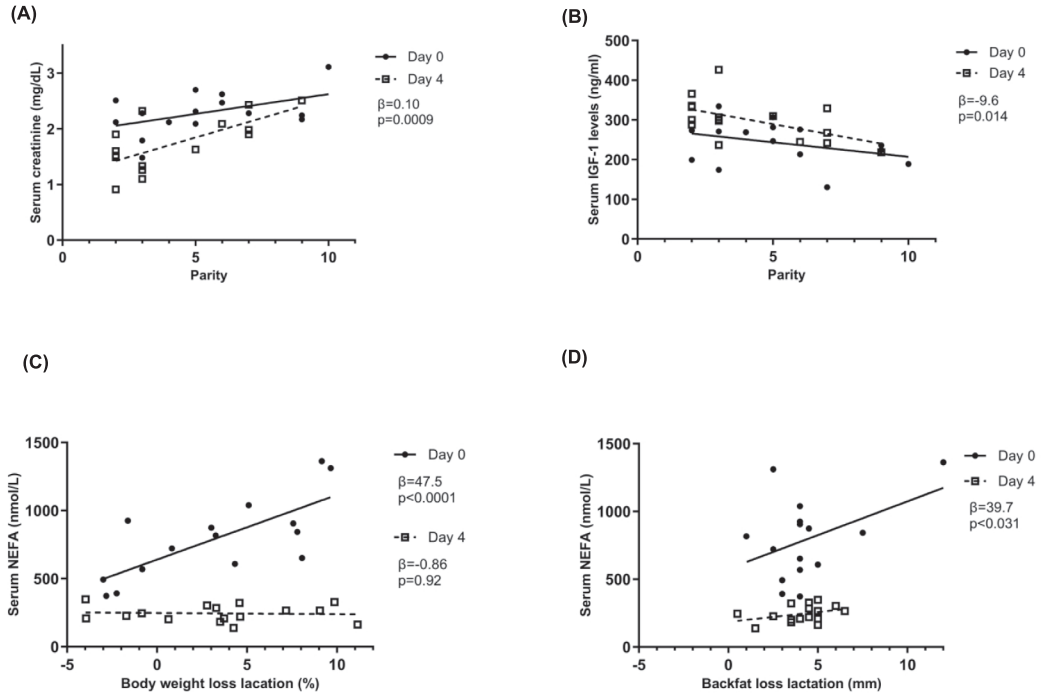

Fig. 1. Plots and regression equations (β) for relations between sow parity and (A) serum creatinine levels (mg/dL) and (B) sow serum IGF1 levels (ng/µl), for relations between (C) sow lactation BW loss (%) and serum NEFA levels (nmol/L), and for (D) sow lactation BF loss (mm) and serum NEFA levels (nmol/L). Day 0 after weaning: ● filled dot; Day 4 after weaning: □ open square. Interactions with Day were only significant for C. Abbreviations: BF = backfat, NEFAs = non-esterified fatty acids.

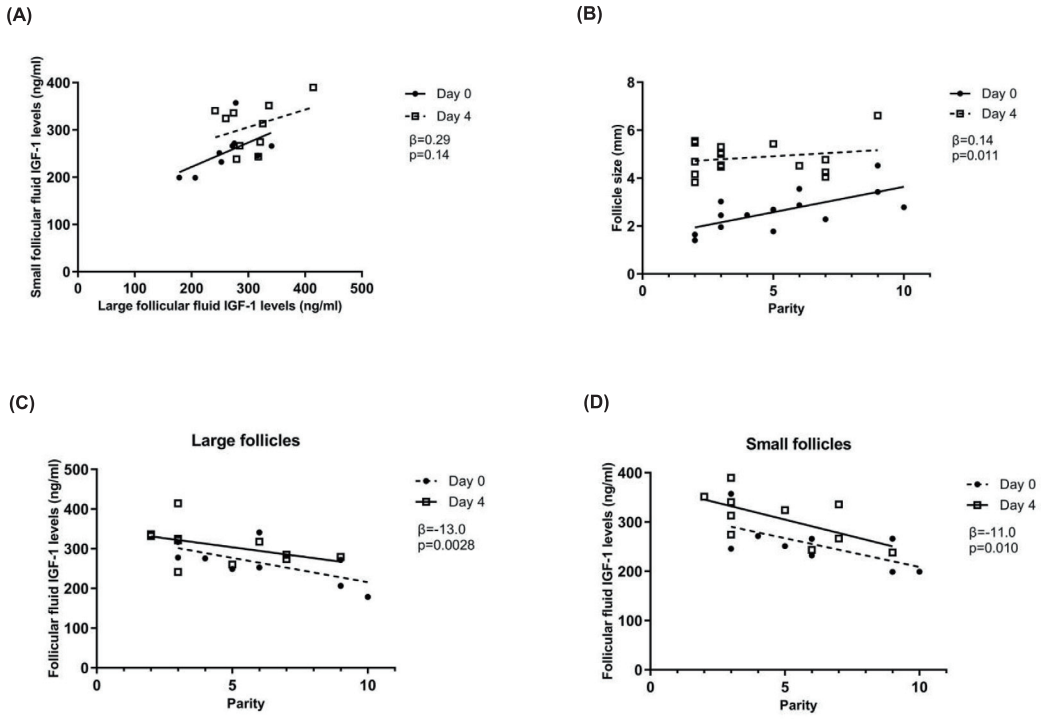

Fig. 2. Plots and regression equations (β) for relations between (A) sow follicular fluid IGF1 levels (ng/μl) in Large vs Small follicles, for relations between (B) sow parity and follicle size[1] (mm), and for relations between sow parity and follicular fluid IGF1 levels (ng/μl) in (C) Large follicles[2] and (D) Small follicles[2]. Day 0 after weaning: ● filled dot; Day 4 after weaning: □ open square. Interactions with Day were never significant. [1]Average follicle size of 30 follicles, being the 15 largest follicles on both the Left and the Right ovary. [2]Measured in the 5 Large and 5 Small follicles of the 15 largest follicles on one ovary.

production of GDF15 in the ovary, as these investigators identified GDF15 in follicular fluid and gene expression in granulosa cells and oocytes, implicating a possible role for GDF15 in follicular development. Unfortunately, we were unable to detect GDF15 in follicular fluid. Taken together, the combined analysis of serum biomarkers levels between Day 0 and Day 4 postweaning and their correlations with BW loss reveals that multiparous sows experience a relatively mild NEB at the time of weaning, which is mostly alleviated by Day 4 postweaning. In other words, after weaning, multiparous sows are quickly capable of changing from a catabolic to an anabolic state to compensate for the lactational NEB.

We further observed that the lower parity sows in our study have higher serum IGF1 levels and lower creatinine levels which were both not affected by BW loss. These parity effects are independent of the day after weaning. One explanation for these effects may be that lower parity sows (parity 2 and parity 3) have not reached maturity yet and are therefore more prone to spare protein for growth. In our study, lower parity sows have smaller follicles; this follicle size is not related to BW loss. Lopes et al. (2020) also found smaller follicles in a higher percentage of sows of parity 1–3 compared to parity 4 and higher, but in their case, this might be related to a higher weight loss in younger sows. Interestingly, sows with higher parity have lower BF losses (β_t = −0.33 mm/parity) and in sows with higher BF losses, the 10 largest follicles tended to be smaller (β_t = −0.13 mm/mm). This might suggest a role for fat mobilisation in follicle development in multiparous sows.

IGF1 is known to play an important role in the follicle and oocyte development (Costermans et al., 2020a,b), and several studies have found relations between them. For instance, Han et al. (2020) report a positive relation between postweaning follicle size and serum IGF1 levels in first and second-parity sows, while Quesnel et al. (1998) show a positive relationship between follicular size and follicular fluid IGF1 levels in primiparous sows at Day 2 after weaning, as did also Costermans et al. (2020b). In another study, Edwards and colleagues (1996) report a positive relation between follicle size and IGF1 concentrations for follicles isolated from 5-month-old gilts and cultured for 6 h. Reduced serum IGF1 levels, such as occur in a severe NEB, result in smaller follicles on Day 2 after weaning (Costermans et al., 2020a,b). These observations all underscore the importance of IGF1 for follicular growth in sows. It seems therefore surprising that in multiparous sows, we do not observe a correlation between either serum or follicle fluid IGF1 concentrations and follicle size. We further observe significant negative correlations between follicular fluid IGF1 levels and parity for both small and large follicles, implicating that with increasing parity the role of IGF1 in follicle growth may become less important. We therefore postulate that in higher parity sows who have stopped growing and in which metabolic condition is thus less affected by lactation than in young sows, reduced IGF1 levels are not limiting follicular growth. The underlying regulatory mechanisms are still poorly understood. Alterations in the sensitivity of growth factor signalling and the interaction of various growth factors may play a role, as is seen in the fruit fly (Texada et al., 2020).

Conclusion

The multiparous sows in this study experience a relatively mild NEB during lactation which is largely alleviated by Day 4 postweaning. This NEB during lactation does not affect the size of the follicles at Day 0 or Day 4 after weaning. Surprisingly, higher parity sows have larger follicles but lower serum and follicular fluid IGF1 levels at both Day 0 and Day 4, suggesting that IGF1 is not limiting follicular growth in mature multiparous sows.

Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.animal.2024.101339.

Ethics approval

The experiment was approved by the Animal Care and Use Committee of Wageningen University (AvD1040020187184) and performed in accordance with national and EU−specific guidelines and standards at the research facility CARUS (Wageningen University, the Netherlands).

Data and model availability statement

None of the data were deposited in an official repository. All data generated during the study are available from the corresponding author by request.

Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Author ORCIDs

Qi Yu: https://orcid.org/0000-0002-2826-8194.
Katja, Teerds: https://orcid.org/0000-0002-0930-1198.
Jaap, Keijer: https://orcid.org/0000-0002-9720-7491.
Nicoline, Soede: https://orcid.org/0000-0003-0296-886X.

CRediT authorship contribution statement

Q. Yu: Writing – original draft, Visualization, Validation, Software, Project administration, Investigation, Formal analysis, Data curation. **K.J. Teerds:** Writing – review & editing, Supervision, Funding acquisition. **J. Keijer:** Writing – review & editing, Supervision, Funding acquisition. **N.M. Soede:** Writing – review & editing, Supervision, Software, Methodology, Funding acquisition.

Declaration of interest

None.

Acknowledgements

The authors are grateful to Marcel Jaklofsky and Bjorge Laurenssen for technical support.

Financial support statement

Human and Animal Physiology Group at Wageningen University & Research, China Scholarship Council 202006380019.

References

Arner, P., 2003. The adipocyte in insulin resistance: key molecules and the impact of the thiazolidinediones. Trends in Endocrinology and Metabolism 14, 137–145. https://doi.org/10.1016/S1043-2760(03)00024-9.

Belstra, B. A., Richert, B. T., Frank, J. W., Kendall, D. C., 1998. Effect of a seven day stair-step feeding regimen versus ad libitum feeding throughout lactation on sow and litter performance. Purdue University Swine Day Report. Purdue University, West Lafayette, IN, USA.

Bergsma, R., Kanis, E., Verstegen, M.W.A., van der Peet-Schwering, C.M.C., Knol, E.F., 2009. Lactation efficiency as a result of body composition dynamics and feed intake in sows. Livestock Science 125, 208–222. https://doi.org/10.1016/j.livsci.2009.04.011.

Caregaro, L., Favaro, A., Santonastaso, P., Alberino, F., Di Pascoli, L., Nardi, M., Favaro, S., Gatta, A., 2001. Insulin-like growth factor 1 (IGF-1), a nutritional marker in patients with eating disorders. Clinical Nutrition 20, 251–257. https://doi.org/10.1054/clnu.2001.0397.

Costermans, N.G.J., Teerds, K.J., Keijer, J., Knol, E.F., Koopmanschap, R.E., Kemp, B., Soede, N.M., 2019. Follicular development of sows at weaning in relation to estimated breeding value for within-litter variation in piglet birth weight. Animal 13, 554–563. https://doi.org/10.1017/S1751731118001684.

Costermans, N.G.J., Soede, N.M., Van Tricht, F., Blokland, M., Kemp, B., Keijer, J., Teerds, K.J., 2020a. Follicular fluid steroid profile in sows: relationship to follicle size and oocyte quality. Biology of Reproduction 102, 740–749. https://doi.org/10.1093/biolre/ioz217.

Costermans, N.G.J., Teerds, K.J., Middelkoop, A., Roelen, B.A.J., Schoevers, E.J., Van Tol, H.T.A., Laurenssen, B., Koopmanschap, R.E., Zhao, Y., Blokland, M., Van Tricht, F., Zak, L., Keijer, J., Kemp, B., Soede, N.M., 2020b. Consequences of negative energy balance on follicular development and oocyte quality in primiparous sows. Biology of Reproduction 102, 388–398. https://doi.org/10.1093/biolre/ioz175.

Costermans, N.G.J., Soede, N.M., Keijer, J., 2022. Physiological and metabolic aspects of follicular developmental competence as affected by lactational body condition loss. Molecular Reproduction & Development 90, 1–12. https://doi.org/10.1002/mrd.23628.

Edwards, J.L., Hughey, T.C., Moore, A.B., Cox, N.M., 1996. Depletion of insulin in streptozocin-induced-diabetic pigs alters estradiol, insulin-like growth factor (IGF)-I, and IGF binding proteins in cultured ovarian follicles. Biology of Reproduction 55, 775–781. https://doi.org/10.1095/biolreprod55.4.775.

Eissen, J.J., Kanis, E., Kemp, B., 2000. Sow factors affecting voluntary feed intake during lactation. Livestock Production Science 64, 147–165. https://doi.org/10.1016/S0301-6226(99)00153-0.

Ford, J.J., Howard, H.J., 1992. Relationships among concentrations of steroids, inhibin, insulin-like growth factor-1 (IGF-1), and IGF-binding proteins during follicular development in weaned sows. Biology of Reproduction 47, 193–201.

Gessner, D.K., Gröne, B., Rosenbaum, S., Most, E., Hillen, S., Becker, S., Erhardt, G., Reiner, G., Ringseis, R., Eder, K., 2015. Effect of a negative energy balance induced by feed restriction in lactating sows on hepatic lipid metabolism, milk production and development of litters. Archives of Animal Nutrition 69, 399–410. https://doi.org/10.1080/1745039X.2015.1075669.

Han, T., Björkman, S., Soede, N.M., Oliviero, C., Peltoniemi, O.A.T., 2020. IGF-1 concentration patterns and their relationship with follicle development after weaning in young sows fed different pre-mating diets. Animal 14, 1493–1501. https://doi.org/10.1017/S1751731120000063.

Heo, S., Yang, Y.X., Jin, Z., Park, M.S., Yang, B.K., Chae, B.J., 2008. Effects of dietary energy and lysine intake during late gestation and lactation on blood metabolites, hormones, milk composition and reproductive performance in primiparous sows. Canadian Journal of Animal Science 88, 247–255. https://doi.org/10.4141/CJAS07060.

Hoving, L.L., Soede, N.M., van der Peet-Schwering, C.M.C., Graat, E.A.M., Feitsma, H., Kemp, B., 2011. An increased feed intake during early pregnancy improves sow body weight recovery and increases litter size in young sows. Journal of Animal Science 89, 3542–3550. https://doi.org/10.2527/jas.2011-3954.

Hoving, L.L., Soede, N.M., Feitsma, H., Kemp, B., 2012. Lactation weight loss in primiparous sows : consequences for embryo survival and progesterone and relations with metabolic profiles. Reproduction in Domestic Animals 47, 873–1061. https://doi.org/10.1111/j.1439-0531.2012.02007.x.

Liu, J., Koenigsfeld, A.T., Cantley, T.C., Boyd, C.K., Kobayashi, Y., Lucy, M.C., 2000. Growth and the initiation of steroidogenesis in porcine follicles are associated with unique patterns of gene expression for individual components of the ovarian insulin-like growth factor system. Biology of Reproduction 63, 942–952.

Lopes, T.P., Padilla, L., Bolarin, A., Rodriguez-Martinez, H., Roca, J., 2020. Ovarian follicle growth during lactation determines the reproductive performance of weaned sows. Animals 10, 1–12. https://doi.org/10.3390/ani10061012.

Lucia, T., Dial, G.D., Marsh, W.E., 2000. Lifetime reproductive performance in female pigs having distinct reasons for removal. Livestock Production Science 63, 213–222. https://doi.org/10.1016/S0301-6226(99)00142-6.

Mosnier, E., Etienne, M., Ramaekers, P., Père, M.C., 2010. The metabolic status during the peri partum period affects the voluntary feed intake and the metabolism of the lactating multiparous sow. Livestock Science 127, 127–136. https://doi.org/10.1016/j.livsci.2009.06.023.

Quesnel, H., Pasquier, A., Mounier, A.M., Prunier, A., 1985. Influence of feed restriction during lactation on gonadotropic hormones and ovarian development in primiparous sows. Endocrinology 117, 2553–2555. https://doi.org/10.2527/1998.763856x.

Quesnel, H., Pasquier, A., Mounier, A.M., Louveau, I., Prunier, A., 1998. Influence of feed restriction in primiparous lactating sows on body condition and metabolic parameters. Reproduction Nutrition Development 38, 261–274. https://doi.org/10.1051/rnd:19980306.

Quesnel, H., Etienne, M., Père, M.C., 2007. Influence of litter size on metabolic status and reproductive axis in primiparous sows. Journal of Animal Science 85, 118–128. https://doi.org/10.2527/jas.2006-158.

Schenkel, A.C., Bernardi, M.L., Bortolozzo, F.P., Wentz, I., 2010. Body reserve mobilization during lactation in first parity sows and its effect on second litter size. Livestock Science 132, 165–172.

Souček, K., Malenovská, A., Kahounová, Z., Remšík, J., Holubcová, Z., Soukup, T., Kurfürstová, D., Bouchal, J., Suchánková, T., Slabáková, E., Hampl, A., 2018. Presence of growth/differentiation factor-15 cytokine in human follicular fluid, granulosa cells, and oocytes. Journal of Assisted Reproduction and Genetics 35, 1407–1417. https://doi.org/10.1007/s10815-018-1230-5.

Texada, M.J., Koyama, T., Rewitz, K., 2020. Regulation of body size and growth control. Genetics 216, 269–313.

Thaker, M.Y.C., Bilkei, G., 2005. Lactation weight loss influences subsequent reproductive performance of sows. Animal Reproduction Science 88, 309–318. https://doi.org/10.1016/j.anireprosci.2004.10.001.

Van den Brand, H., Prunier, A., Soede, N.M., Kemp, B., 2001. In primiparous sows, plasma insulin-like growth factor-I can be affected by lactational feed intake and dietary energy source and is associated with luteinizing hormone. Reproduction Nutrition Development 41, 27–39. https://doi.org/10.1051/rnd.

Wang, D., Day, E.A., Townsend, L.K., Djordjevic, D., Jørgensen, S.B., Steinberg, G.R., 2021. GDF15: Emerging biology and therapeutic applications for obesity and cardiometabolic disease. Nature Reviews Endocrinology 17, 592–607. https://doi.org/10.1038/s41574-021-00529-7.

Whitley, N.C., Barb, C.R., Utley, R.V., Popwell, J.M., Kraeling, R.R., Rampacek, G.B., 1995. Influence of stage of the estrous cycle on insulin-like growth factor-I modulation of luteinizing hormone secretion in the gilt. Biology of Reproduction 53, 1359–1364. https://doi.org/10.1095/biolreprod53.6.1359.

Wientjes, J.G.M., Soede, N.M., Laurenssen, B.F.A., Koopmanschap, R.E., Van Den Brand, H., Kemp, B., 2013. Insulin-stimulating diets during the weaning-to-estrus interval do not improve fetal and placental development and uniformity in high-prolific multiparous sows. Animal 7, 1307–1316. https://doi.org/10.1017/S1751731113000566.

Zak, L.J., Xu, X., Hardin, R.T., Foxcroft, G.R., 1997. Primiparous sow on follicular development and oocyte maturation. Journal of Reproduction and Fertility 110, 99–106.