Pathophysiology of **anestrus** in sows

Reproductive seasonality syndrome often appears during summer and early autumn. However, anestrus does not only appear in summer months.

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Anestrus is defined as the absence of cyclical sexual activity. This has an important physiological base in sows which is inherited from the reproductive seasonality of their wild boar ancestors. In non-domestic pigs, temperature, light, and the availability of food control the function of the HHO axis and help them 'select' the best time of year for reproductive success and survival of their piglets. Female wild boar usually only have ovarian activity from November to April (Mauget, 1987).

Reproduction is a 'luxury' function and so, if a sow has received many concomitant and repetitive stressors over time, her brain will consider that moment not to be the best time for reproductive success.

The domestic sow

Over the years, porcine domestication has been modifying this tendency towards reproductive seasonality in sows, to the point that females are now considered to exhibit continuous polyoestrous behaviour. Despite this, the appearance of reproductive seasonality syndrome frequently appears during the summer and early autumn. This syndrome is characterised by a decrease in all their reproductive parameters (*clinical presentation 1*), including an increase in the percentage of nulliparous, primiparous, and multiparous sows in summer anestrus. Hormonally, this seasonality is accompanied by an imbalance in the hypothalamus–hypophysis–ovary (HHO) axis which compromises correct ovarian function, preventing the follicles from developing normally and therefore, inhibiting ovarian cyclicity—i.e., preventing ovulation and the formation of corpora lutea.

However, we should not think that anestrus can only appear in summer; it presents throughout the year at some farms. This is because reproduction is a 'luxury' function and so, if a sow has received many concomitant and repetitive stressors over time, her brain will consider that moment not to be the best time for reproductive success and will inhibit the HHO axis, which interferes with follicular development and maturation and, therefore, preventing her from going into heat.

Clinical presentation 1. Reproductive seasonality syndrome: alteration of the reproductive parameters of sows between June and September.

- Increased percentage of piglets with delayed onset of puberty (prepubertal anestrus)
- Increased postpubertal anestrus before the first cover
- Alteration of hormonal levels during heat
  - Increased 'silent heat' or sub-oestrus
- Less chance of maintaining pregnancy and increased return to heat:
  - Decreased fertility
  - Increased embryonic mortality
  - Autumn abortion syndrome
- Farrowings last longer
- Increased number of stillborn piglets
- Increase in the percentage of sows with ovarian inactivity after weaning their piglets (post-weaning anestrus)
- Increased frequency in the appearance of isolated ovarian cysts

Incidence

A proportion of 7% post-weaning sows in anestrus is considered normal (Rodríguez-Estévez, 2010). When this value is exceeded, problems appear on the farm which must be solved as soon as possible. Changing or improving a single stressor will not solve the problem. We must ensure that sows are properly housed, fed, and handled. Hormonal treatments with gonadotropins can sometimes be used to treat these animals and induce heat (Falceto *et al*., 2005; Ubeda *et al*., 2013), but otherwise, this reproductive failure will end with the culling of sows diagnosed with anestrus on the farm.

Table 1 shows the findings from several authors regarding the importance of reproductive failure in terms the different reasons for culling breeding sows on pig farms. The latest data, from Iborra *et al*. (2017), indicate that reproductive problems constitute almost 50% of the causes of breeder waste on Spanish pig farms (*Figure 1*).

Consequences of anestrus

The economic losses produced by anestrus are due to:

- The increased number of non-productive days of sows on the pig farm (*clinical presentation 2*).
- The increased expense in terms of hormonal treatments.
- The culling of non-cyclical sows at the slaughterhouse, often without them having produced a return on investment or having only had a few farrowings.

In addition to the above, not all females culled because of anestrus are infertile. When ovaries from these sows are analysed at the slaughterhouse, it can be seen that approximately 40–60% of them show cyclical activity (Falceto, 2004 a; Falceto, 2015) and are suitable for reproduction. This sub-group of sows sent for culling for anestrus will have been included because of human error, probably because their heat went unnoticed or was silent (sub-oestrus). The appropriate term for these cases is **pseudoanestrus**. In **true anestrus** the ovaries do not show cyclical activity (Falceto, 2004 b and c). *Tables 2* and *3* differentiate anestrus and pseudoanestrus, as well as their causes.

Study	Reproductive failure (%)	Problems during farrowing (%)	Low productive performance (%)	Lactation problems (%)	Locomotor problems (%)	Disease (%)	Old age (%)	Death (%)
Pomeroy, 1960.	21.4	2.0	22.4	6.1	ND	13.3	17.1	ND
Jones, 1967.	8.8	ND	ND	5.6	9.4	2.4	2.2	10.1
Dagorn and Aumaître, 1979.	39.2	4.0	8.4	ND	8.8	ND	27.2	6.5
Svendsen *et al.*, 1980.	28.8	ND	10	ND	15	ND	3.9	ND
Pattison *et al.*, 1980.	37.5	ND	13.8	ND	11.8	ND	24.4	ND
Joo and Kang, 1981.	32.6	ND	15.7	ND	9.7	ND	16.7	ND
Muirhead, 1981.	35.4	2.8	ND	5.0	10.8	ND	28.2	4.6
Stone, 1981.	12.9	1.6	20.6	8.9	11.0	4.2	33.4	ND
Friendship *et al.*, 1986.	23.7	2.3	14.5	9.0	11.8	2.5	19.2	3.0
D'allaire, 1987.	32.4	7.2	16.8	ND	8.9	1.6	14.0	11.6
Dijkhuizen *et al.*, 1989.	34.2	ND	20.1	ND	10.5	ND	11.0	ND
Stein *et al.*, 1990.	29.6	5.0	9.4	8.8	11.0	0.8	17.9	10.7
Cederberg and Jonsson, 1996.	29	ND	1	13	14	ND	8	7.5
Kangasniemi, 1996.	28.2	2.4	14.4	1.9	13.5	1.4	16.8	3.2
Paterson *et al.*, 1996.	21.3	ND	2.3	1.6	9.3	3.5	7.2	5.0
Pedersen, 1996.	34.5	ND	4.6	ND	6.1	ND	18.8	12.3
Sehested and Schjerve, 1996.	28.7	1.9	4.8	0.9	10.2	4.9	11.3	4.2
Boyle *et al.*, 1998.	29.8	ND	11.1	ND	11.3	7.4	31.3	6.6
Lucia *et al.*, 2000.	33.6	ND	20.6	ND	13.2	3.1	8.7	7.4

ND = no data

Table 1. Summary of different studies on the causes for the culling of breeders on farms (adapted from Stalder *et al.*, 2004).

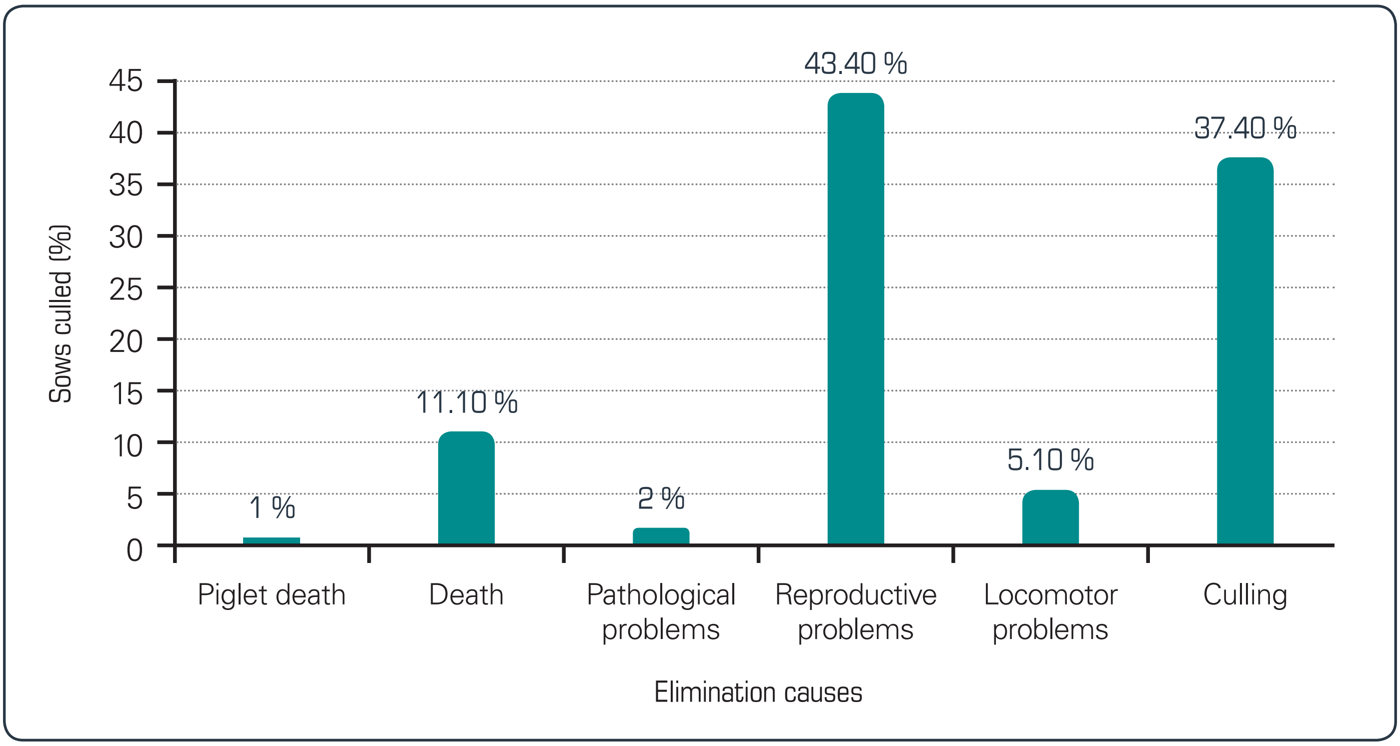

Figure 1. Main causes of the culling of breeding sows in Spain (Iborra *et al.*, 2017).

Clinical presentation 2. Non-productive days on pig farms include the following periods.

- Waiting time until the first cover (prepubertal anestrus and voluntary waiting until the first insemination in the third heat).
- Gestation time (110–119 days).
- Lactation time (21–28 days).
- Weaning-coverage interval < 7 days.
- Weaning-coverage interval > 7 days (post-weaning anestrus).
- The time taken for an inseminated, non-pregnant sow to return to heat and become pregnant.
- Time taken from the decision to cull a sow until it is picked up by the truck to transport it to the slaughterhouse.

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True anestrus	Pseudoanestrus
Delayed puberty in nulliparas	Inadequate heat detection
Pubertal females that do not go into heat (postpubertal anestrus)	
Delayed return to heat after weaning in primiparous and multiparous sows	Ovarian pathology
Inseminated, non-pregnant females that do not come into heat	Gestation not detected

Tabla 2. Situaciones en la granja porcina que cursan con ausencia de celo.

True anestrus	Pseudoanestrus (due to heat-detection failure)
Persistent stress	Inadequate staff training
Seasonal infertility	Inadequate return-to-oestrus
Inadequate body condition	Inadequate equipment and facilities
Predisposition of the primiparas	Silent and unexpected heats

Table 3. Main causes of anestrus and pseudoanestrus in sows.

Types of anestrus

True anestrus in sows can be considered physiological or pathological, depending on the age and the reproductive moment at which the problem appears (Falceto, 2004 a).

An ovarian follicle consists of an oocyte surrounded by a larger or smaller number of cells. During their development they form a structure called a follicular antrum which is produced by the accumulation of liquid inside the follicle.

True anestrus

Anestrus is considered to be physiological (*clinical presentation 3*) when it occurs during non-reproductive times of the sow's life, characterised by absence of ovarian activity and therefore of the symptoms of heat. This occurs before puberty, during pregnancy, during lactation, and immediately after weaning.

Pathological anestrus

If the physiological anestrus is prolonged (delayed puberty for more than 8 months or postweaning anestrus for more than 7 days) or if the sow does not return to heat after having presented a heat (whether or not she was inseminated), we interpret it as pathological anestrus (*clinical presentation 3*) because, while the ovaries are not working, it is impossible to start the reproductive process.

<table>
<tr><th colspan="3">1. True anestrus</th></tr>
<tr><th>Physiological anestrus</th><th colspan="2">Pathological anestrus</th></tr>
<tr><td rowspan="2">• Prepubertal
• Gestational
• Lactational
• Postweaning, up to a maximum of 7 days</td><td>Nulliparous (older than 8 months of age)</td><td>Primiparous and multiparous</td></tr>
<tr><td>• Delayed puberty:
  • Agenesis or ovarian hypoplasia
  • Prolonged prepubertal anestrus
• Pubertal females that do not come into heat (postpubertal anestrus)</td><td>• Delayed return to heat 7 days post-weaning.
• Inseminated and non-pregnant sows that do not come out in heat.</td></tr>
<tr><th colspan="3">2. Pseudoanestrus</th></tr>
<tr><td colspan="2">• Sub-oestrus (silent heat)
• Pregnant female noted as not pregnant
• Heat-detection failure in:
  • Covering room
  • Gestation room
  • Farrowing room</td><td>• Ovarian pathology:
  • Polycystic ovarian degeneration:
    - Luteinised follicular cysts
    - Luteal cysts
  • Persistent corpus luteum
  • Luteoma</td></tr>
</table>

Clinical presentation 3. Types of anestrus.

Control of ovarian follicular development in cyclic sows and in anestrus

The functions of the ovary are the production of **fertilisable oocytes** and the balanced and cyclical production of steroid hormones. Both of these functions are required in order to achieve heat, coverage, and the development of a pregnancy until farrowing. Ovarian follicles allow this dual function of oogenesis and steroidogenesis to be carried out.

An ovarian follicle consists of an oocyte surrounded by a larger or smaller number of cells. During their development they form a structure called a **follicular antrum** which is produced by the accumulation of liquid inside the follicle. The presence or absence of the antrum determines whether the follicles will be preantral or antral.

- **Preantral follicles** contain a primary oocyte (2n) arrested in prophase at the stage of the first meiotic division. Follicular growth at this stage depends only on intraovarian factors and is independent of the gonadotropic control exerted by the hypothalamus and pituitary gland.
- **Antral follicles** have a cavity filled with follicular fluid which is prominent on the ovarian surface. These may be small (2–4 mm), medium (4–6 mm), or large (6–12 mm). The growth of antral follicles is controlled by the HHO axis.

Gonadotropin-releasing factor (GnRH) controls the production of follicle-stimulating hormone (FSH) and luteinising hormone (LH). FSH stimulates follicular development until it reaches a medium size, while LH is required for terminal follicular growth into a preovulatory follicle (Driancourt, 1995).

In the following section we will describe the control of follicular development in cyclical sows and in sows in anestrus.

Cyclic sows

Domestic sows go into heat and ovulate every 21 days. Small and medium preantral and antral follicles can be found during every phase of the ovarian cycle (proestrus, oestrus, metoestrus, and anestrus), but large follicles are only present during proestrus and oestrus. There are no differences between the number of small, medium, and large follicles present in the left and right ovaries of sows during the different phases of their sexual cycle (Falceto, 1992).

If the sow has a balanced HHO axis, weaning itself or a decrease in progesterone at the end of anestrus induces the increase in FSH and LH gonadotropins which recruits medium-sized ovarian follicles for growth during **proestrus**. The increase in follicle size, and therefore in the levels of oestrogens and inhibin, decreases these gonadotropins which prevents the recruitment of further medium-sized follicles and allows selection of 10–20 large follicles which will continue to grow. At the end of **oestrus**, the positive feedback from oestrogens induces the preovulatory LH peak. Following this LH spike, completion of the first meiotic division and ovulation of a secondary oocyte (n) occurs. After this, any follicle of any size that failed to ovulate then undergoes atresia (atrophy).

After the formation of a clot at the point of ovulation (corpora *hemorrhagicum*) during **metoestrus**, the corpora lutea progressively start to produce progesterone during anestrus. If the sow is not pregnant, progesterone progressively decreases during **anestrus** due to the luteolytic effect of prostaglandins, and follicular recruitment starts again so that the sow will come into heat again.

Sows in anestrus

The ovarian follicles of sows in **true anestrus** always measure less than 6 mm (*figure 2*). Prolactin modulates the steroidogenesis of these small and medium follicles. Microscopically, follicular growth always ends in atresia. Corpora *hemorrhagicum* and corpora lutea can never be found in the absence of ovulation. The presence or absence of corpora *albicantia* will depend on whether there had been luteal activity during other recent cycles. The remains of previous intense cyclical ovarian activity can be seen as connective tissue grooves and scarring in old sows in anestrus.

The number and size (very small, small, and medium) of the ovarian follicles depends on how well connected the ovaries are to the hypothalamic–pituitary axis. The absence of this connection is referred to as **deep anestrus** and only follicles smaller than 2 mm can be found in these cases (*figure 3*). If the ovary is smooth and follicles are absent at the microscopic level, the pathology is likely congenital **ovarian hypoplasia**, which also presents with anestrus and is usually associated with infantilism of the rest of the genital apparatus.

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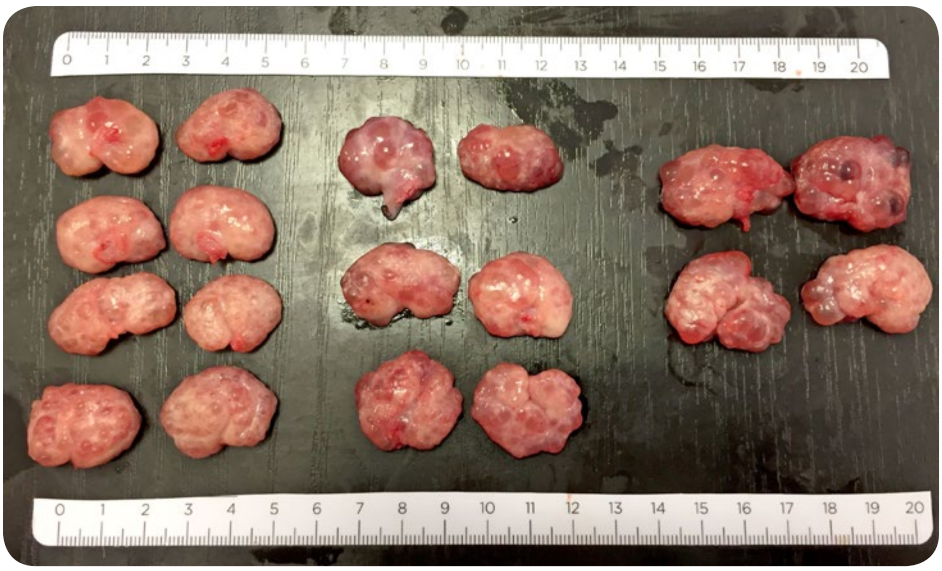

Figure 2. Ovarian follicles from sows in true anestrus.

It may be possible to stimulate terminal follicular growth in the ovaries of females in anestrus so that they come into heat only by using **equine chorionic gonadotropin (eCG) and human (hCG)**. Exogenous eCG acts as a pituitary FSH and while hCG acts as a pituitary LH. These hormones not only serve as a treatment for anestrus, they are also often used in summer months to help prevent seasonal anestrus in both nulliparas after withdrawal of progestogen and in multiparas after weaning.

The number and size (very small, small, and medium) of the ovarian follicles depends on how well connected the ovaries are to the hypothalamic–pituitary axis.

Figure 3. Follicles in deep anestrus.

Diagnosis of ovarian cyclicity

Anestrus is clinically diagnosed when sows do **not go into heat**. In dubious cases, ovarian cyclicity can be diagnosed by ovarian ultrasound and by determining progesterone hormone levels. Correct differential diagnosis of anestrus and pseudoanestrus can prevent productive sows from being sent to the slaughterhouse.

Abdominal ultrasound

An **abdominal ultrasound** allows large follicles and ovarian corpora lutea to be visualised. In nulliparous females this technique allows the level of uterine development to be verified in order to determine if they have reached puberty or not.

Determination of progesterone levels

Progesterone can be determined in a drop of plasma or blood serum. Commercial ELISA tests for this purpose are available that can be performed on the farm itself. Progesterone levels remain at a low level (< 2.5 ng/ml) for 5 days before oestrus; during oestrus and one day afterwards, it begins to increase on day 2 of the cycle and reaches its maximum values of 25–35 ng/ml on day 10. Progesterone levels remain high until day 14–16 when they begin to rapidly decrease to reach their basal levels within 48 hours. A female in true anestrus will have very low progesterone production (< 2.5 ng/ml) at all times.

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Factors influencing the appearance of summer anestrus in porcine species

Multiple factors influence the balance of the HHO axis (*clinical presentation 4*), and although the causes of the appearance of summer anestrus in porcine species remains unclear, it seems that temperature and nutrition may be the most important factors.

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Clinical presentation 4. Factors that influence the appearance of anestrus in porcine species.

- Nutrition and body condition
- Number of deliveries: nulliparous, primiparous, or multiparous
- Reproductive seasonality inherited from their wild boar ancestors:
  - Photoperiod
  - Temperature
- Persistent stress caused by management failures:
  - Poor accommodation design
  - Feeding restrictions
  - Sudden changes in diet
  - Hygienic-cleanliness treatments
  - Social factors:
    - Interactions with other females
    - Unfamiliar noises
    - Change in caregivers
  - Environmental factors:
    - Sudden changes in temperature
    - Humidity
    - Air currents
    - High environmental levels of ammonia

Diet

Wild boars go into a period of heat between September and December, and so the consequent farrowing period runs from January to April. In Mediterranean ecosystems, the heat season usually coincides with the time that acorns naturally fall, mainly in late October and early November. However, it is important to highlight that supplementation of their food intake during other seasons, especially in the summer, can also cause the females to come into heat (Fernández Llario, 2005). These data indicate that food availability is a particularly important factor in the appearance of anestrus in swine.

Food is not a limiting factor on pig farms because farmed animals usually have an abundant and balanced diet. However, many sows eat less during the summer because the high temperatures decrease their appetites. This is especially true of primiparous sows because their physical capacity to ingest food is lower than multiparas and their endocrine systems are still immature and growing (Tummaruk *et al.*, 2007; Auvigne *et al.*, 2010).

Lower feed consumption results in weight loss and inadequate body condition in sows and can determine metabolic alterations and HHO axis endocrine dysfunctions. In order to come into heat, sows require LH for terminal follicular growth. The frequency and amplitude of LH release is insufficient in sows in a catabolic state (Baidoo *et al.*, 1992; De Rensis and Kirkwood, 2017).

Temperature

As a species, swine are very sensitive to high temperatures because they have very few sweat glands and only lose heat by convection via air or water or by conduction to cooler surfaces. This stress can be seen as a response in the form of tachypnoea, increased rectal temperature, decreased feed intake, and a slower growth rate.

During heat stress, epinephrine stimulates the hypothalamus, which in turn, determines the secretion of corticotropin-releasing factor (CRF). Pituitary adrenocorticotropic hormone (ACTH) induces the release of glucocorticoids and small amounts of mineralocorticoids. Corticosteroids inhibit the HHO axis, lowering serum levels of FSH and LH, and therefore also reducing oestrogen and progesterone levels (Britt *et al.*, 1985). Other pituitary hormones such as growth hormone, thyrostimulin, and prolactin are also modified by ACTH. Ovarian dysfunctions such as anestrus and silent heat appear as a consequence of this endocrine imbalance.

Increased body temperature, decreased appetite, and increased growth hormone levels may be associated with reduced activity of aromatase—a hormone that mediates the conversion of androgens to oestrogens in antral follicle granulosa cells (Xu *et al.*, 1995). As a consequence of lower oestrogen levels, the symptoms of heat may be weaker in both nulliparous and multiparous sows. These silent heats are difficult to identify and are only diagnosed on farms with very experienced personnel and excellent heat-detection protocols. On farms where it is not diagnosed, a high percentage of females in pseudoanestrus are treated with gonadotropic hormones or are unnecessarily culled at the slaughterhouse.

Thus, one of the most effective ways to prevent pseudoanestrus is to control the temperature and humidity of farms. Sows must be kept cool and fresh water must always be available to them. In addition, stress caused by management failures should be reduced and the welfare of breeding sows should be increased.

Recommendations

- To minimise the percentage of sows in anestrus, it is advisable to offer a diet balanced in energy, protein, minerals, and vitamins and which is adapted to the different needs of each sow, both during pregnancy and lactation. In addition, sows should be encouraged to eat throughout lactation.
- Another alternative in very underweight females is the administration of altrenogest for 8 days, starting on the day before weaning. In this way, the sow recovers her body condition and goes into heat after the withdrawal of progestogen.

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