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Pharmacological intervention in swine reproduction

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Summary

If gilts are known to be cyclic, the options to control estrus are breed-and-abort or feeding allyl trenbolone (Regumate®). For breed and abort, terminate pregnancy 25–30 days postbreeding with two injections of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 6–8 hours apart. Gilts should return to estrus within 4–6 days with normal fertility. When feeding allyl trenbolone, you must ensure individual feeding so that gilts receive at least 15 mg (Regumate®) per day. There is probably no problem with overdosing, but underdosing (<13 mg per day) may cause cystic follicles. If gilts are known to be prepubertal, gonadotropin (PG600®) works well. If inducing estrus with gonadotropin, breed at the induced estrus but expect some possible depression in reproductive performance. If the gilts' cyclic status is unknown, gonadotropin can be used but there may be risks. If gilts are having silent heats, cystic follicles may form and the gilts will become infertile—treat for 14–18 days with allyl trenbolone followed by gonadotropin at withdrawal. Gonadotropin also works well after weaning of the first litter. Injection can be administered on the day of, or the day after, weaning. For farrowing induction, determine gestation length on each farm and do not inject $PGF_{2\alpha}$ more than 2 days before due date. Inject a half-dose of $PGF_{2\alpha}$ intravulvally at the beginning and end of the day (split-dose). Do not use oxytocin unless at least one pig has been born or continual supervision is practiced.

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This production tool provides practical guidelines for pharmacological intervention in swine reproduction and cites references to illustrate potential outcomes. The areas of reproduction to be addressed are the induction and control of estrus, interventions at breeding, and the control of farrowing. As an introductory statement, I wish to emphasize my belief that, where possible, the most rational strategy is one of no intervention. However, modern swine production practices are often dictated by economic forces that require some degree of strategic control. The swine practitioner's role is to know when and how best to intervene in order to gain the optimum return for the intervention dollar.

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Exogenous hormones are an invaluable tool for the swine practitioner but if used inappropriately may result in production problems. When a reproduction problem is encountered, first look for and try to correct underlying causes before resorting to hormone administration. For the strategies described in this text, it is assumed that management problems either were not identifiable or were not correctable.

Controlling onset of estrus

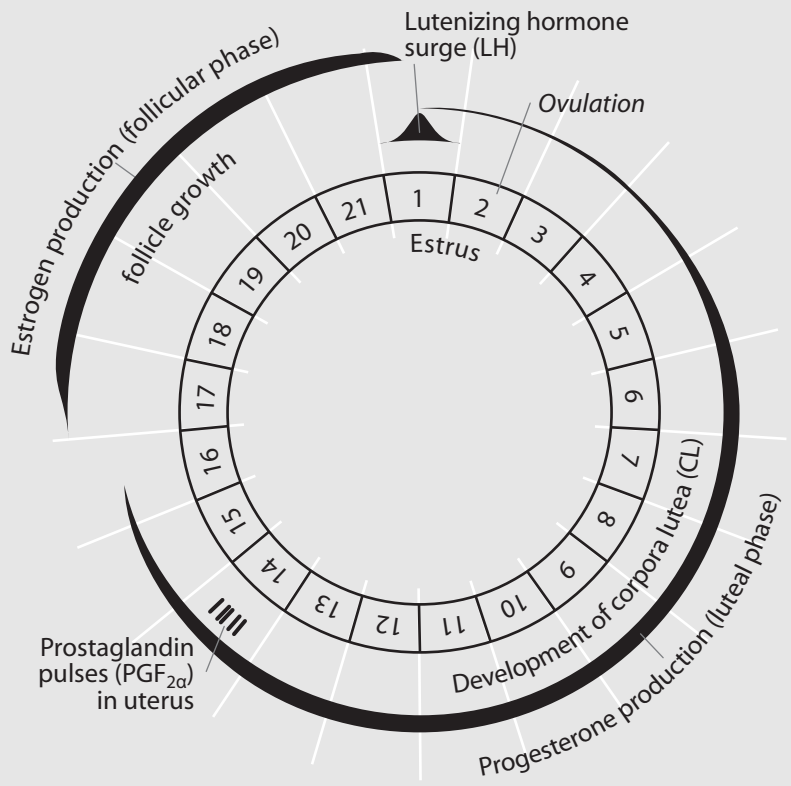
It is essential to thoroughly understand the estrous cycle before considering intervention. In simple terms, the 21-day porcine estrous cycle is composed of an approximately 16-day luteal phase and a 5-day follicular phase (Figure 1). During the luteal phase, the ovaries (corpora lutea) produce progesterone, which limits follicular development to the medium-sized follicle stage and so prevents the onset of estrus. At about 12–14 days of the luteal phase, uterine production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) causes regression of corpora lutea and so terminates progesterone production. Removing the progesterone block allows resumption of appropriate secretory patterns of the pituitary gonadotropins, luteinizing hormone (LH), and follicle stimulating hormone (FSH) which, in turn, allows ovarian follicular development to be completed with the production of estrogen, ultimately resulting in behavioral estrus. In weaned sows, the wean-to-estrus interval is equivalent to the follicular phase of the estrous cycle. Approximately coincident with the onset of estrus, there is a surge release of LH, which causes a cascade of events within the follicle, including a switch from estrogen to progesterone production and also the production of intrafollicular $PGF_{2\alpha}$, culminating with ovulation.

Cyclic gilts

If gilts are known to be cyclic, the options for controlling estrus are limited to breed-and-abort and the feeding of allyl trenbolone. A prolonged luteal phase (pseudopregnancy) with induced luteolysis can also be induced, but this process is still largely experimental. Note that, unlike cattle, a single injection of $PGF_{2\alpha}$ in pigs will not induce luteolysis before day 12 of the estrous cycle and so is of limited value. However, if required, one can reduce the length of the estrous cycle by 2–5 days by injecting $PGF_{2\alpha}$ every 24 or 36 hours between days 6 and 10 of the cycle.[1]

For breed-and-abort, a successfully established pregnancy results in the endogenous production of progesterone, which will block estrus until pregnancy is terminated. In theory, pregnancy can be terminated at any time prior to term and the gilt should return to estrus 5–6 days later (but this may take as long as 10 days). However, uterine involution must occur after pregnancy. Although a gilt may return to estrus, if uterine involution is incomplete it may limit subsequent litter size by

Figure 1



Endocrine mechanisms of the normal estrous cycle

adversely affecting embryo/fetal survival. Also, terminating pregnancy after 25–30 days may raise ethical and aesthetic issues. If undertaken, terminate pregnancy 25–30 days postbreeding with a split dose of $PGF_{2\alpha}$ (i.e., a half dose intravulvally a.m. and then again p.m.). Gilts should return to estrus in 4–6 days with normal fertility.[2,3]

Feeding allyl trenbolone (Regumate®) is an effective way to control estrus.[4] Allyl trenbolone is an orally active progestagen; i.e., it mimics the biological activity of progesterone. While being fed, allyl trenbolone does not prevent normal luteolysis, but will continue to block the onset of estrus after luteolysis occurs. Ideally, gilts should be individually fed so that they consume at least 15 mg per day. While there is probably no problem with overdosing (except economic), underdosing allyl trenbolone (<13 mg per day) may cause cystic follicles.[5,6] Anecdotal evidence suggests variable responses to allyl trenbolone in the field—some producers report having good success while others do not. In all likelihood, producers who observe a poor response to allyl trenbolone treatment are not using it correctly. As stated above, a minimum intake of 15 mg per day by every treated gilt is essential. Since allyl trenbolone needs to be fed only from luteolysis, if cycle dates are known you can minimize allyl trenbolone feeding by only providing it from day 14 of the estrous cycle until 5 days before gilts are scheduled to be bred. Expect 90%–95% of gilts to achieve estrus on days 4–8 after the last feeding.[7]

Prepubertal gilts

In the start-up phase of large commercial units, it is important to produce pigs as soon as possible to maximize cash flow. In practice, this often means breeding gilts at their pubertal estrus in order to meet weekly breeding targets, even though research results suggest that this will reduce first litter sizes. If gilts are known to be prepubertal, treating with gonadotropin (e.g., PG600®) following the manufacturer's recommendations is quite effective for inducing estrus and ovulation. The exogenous gonadotropins act in the same manner as endogenous gonadotropins during the follicular phase of the estrous cycle (Figure 1). However, up to 30% of treated gilts do not show behavioral estrus (but will probably ovulate).[8,9] Also up to 30% of those that demonstrate behavioral estrus will fail to cycle normally (i.e., will have an irregular return).[9] Therefore, if inducing with gonadotropin, I recommend breeding at the induced estrus, but expect possible depression in farrowing rate and/or litter size.

This recommendation was recently tested by the Alberta Pork Research Centre.[9] A 1200-sow startup herd reported a problem of delayed puberty, causing a failure to achieve breeding targets. The gilts in the replacement pool appeared well developed (>100 kg) at the site visit, and boar exposure was being managed appropriately (i.e., mature boars and direct contact). Because so many gilts were failing to achieve estrus, the clinical diagnosis was a failure to reach puberty rather than the occurrence of silent heats. Therefore, an intervention strategy employing gonadotropin was implemented. During a 19-day period, gilts in alternate pens received gonadotropin (PG600®) intramuscularly (IM), with remaining gilts serving as controls. Daily boar exposure continued for all gilts. At detection of estrus, gilts that received gonadotropin were assigned to be bred or allowed to cycle, depending on gilt breeding requirements. Control gilts were always bred at their first observed estrus. All breedings were by artificial insemination (AI) at the detection of estrus and 24 hours later.

Table 1

Performance of gilts bred at a PG600®-induced or natural first estrus

	Control	PG600®	*P*
Service-ready gilts	37.5%	78.0%	.0001
Entry-to-service, d	41.5 ±1.8	39.8 ±1.4	–
Service age, d	192.6 ±6.2	185.9 ±1.7	.02
Farrowing rate	88.6%	74.4%	.01
Litter size (total)	9.7 ±0.3	9.4 ±0.3	–

Adapted from Kirkwood, et al.[9]

Of the gonadotropin-treated gilts, 78% displayed estrus within 7 days (Table 1). Of the 171 gilts included in the study, 133 were bred and 99 conceived. Of the 34 nonconceiving gilts, 23 had regular returns and 11 had irregular returns. Of 38 nonbred gilts, 24 had a regular return-to-estrus and 14 had irregular returns. During this period, fewer control gilts were bred (84 of 224; $P<.0001$) but their conception rate was higher ($P<.01$) than for gonadotropin-treated gilts. The entry-to-service interval was similar for bred gonadotropin-treated and control gilts, but age at first service was lower ($P<.02$) for gonadotropin-treated gilts compared to controls (Table 1). Subsequent litter size was not affected by gonadotropin treatment (Table 1).

These data demonstrate that gonadotropin may provide an effective way to achieve breeding targets. However, when gilts are bred at the induced estrus, a significant depression in farrowing rate can be expected. Using the calculation:

$$\text{proportion of gilts bred} \times \text{farrowing rate} \times \text{litter size},$$

as a crude measure of gilt productivity, piglet production from PG600®-treated gilts was:

$$0.78 \times 0.744 \times 9.4 = 5.46 \text{ pigs},$$

while from controls production was:

$$0.375 \times 0.886 \times 9.7 = 3.22 \text{ pigs}.$$

This indicates that the ability to achieve breeding targets using gonadotropin outweighs a possible depression in fertility.

Gilts of unknown status

If the gilts' cyclic status is unknown, gonadotropin can be used successfully,[10] but there may be risks. If gilts are having silent heats and are actually cyclic, cystic follicles may form after gonadotropin treatment (Foxcroft GR, personal communication, 1997). However, in contrast, in studies in which gonadotropins have been administered with the intention of inducing accessory corpora lutea at various days during the estrous cycle, the occurrence of cystic follicles was not mentioned and so, presumably, were not evident.[11,12] Therefore, it is possible that cyclic gilts that have cystic follicles after gonadotropin treatment may have already been cystic at the time of gonadotropin injection. Further, it is possible that gilts that have silent heats respond to gonadotropic stimulation differently than gilts with normal cycles. The safe way with these gilts is to provide 14–18 days of allyl trenbolone, followed by gonadotropin at withdrawal. Doing this will greatly reduce/eliminate luteal phase gilts. The risk here is that you waste the cost of gonadotropin if they are cyclic or the cost of allyl trenbolone if they are not. Using $PGF_{2\alpha}$ is of no value because <15% of gilts can be expected to be at the 12- to 15-day point of their cycle.

A common scenario is a small proportion of incoming gilts (5%–15%) failing to show estrus within a reasonable period after entry (e.g., 28 days). It has been suggested that these gilts are either having a silent estrus or are prepubertal but relatively infertile.[4] In either case, an argument can be made that they should be culled. However, if there is pressure to keep them, and using allyl trenbolone (as outlined in the previous paragraph) is not possible, then a "last chance" injection of gonadotropin can be administered and they can be bred at the induced estrus. Any gilt failing to exhibit estrus by 7 days should be culled. If a well-developed gilt fails to show a natural estrus and then subsequently fails to respond to gonadotropic stimulation, she is not a reasonable candidate for becoming a productive and profitable sow. Any bred gilt that fails to conceive to the service should also, arguably, be culled as infertile.

Table 2

Effect of PG600® at weaning on performance of primiparous sows

	Control	PG600®	*P*
Number of sows	641	609	–
Bred by 7 d	326 (50.0%)	442 (72.6%)	.001
Bred by 25 d	480 (74.9%)	514 (84.4%)	.001
Wean–estrus, d	8.7 ±0.3	6.7 ±0.2	.001
Farrowing rate	86.9%	86.0%	.4
Second litter size, total born	10.5 ±.02	9.8 ±0.2	.02
Second litter size, live born	10.0 ±0.2	9.3 ±0.2	.01
Pigs per weaned sow*	4.56	6.12	–

* equal to bred by 7 d × farrowing rate to first service × total pigs born from that service

Weaned sows

Gonadotropins are most frequently used in sows at the weaning of the first litter, when longer and more variable wean-to-estrus intervals are often encountered. Several studies have examined this area and all agree that gonadotropin treatment results in a shorter and more synchronous onset of the postweaning estrus (Table 2).[13–16] The day of injection (i.e., at weaning or the next day) has no effect on the response obtained.[17] Although gonadotropin is an excellent tool for inducing a synchronous postweaning estrus, you should examine the herd records before using it to determine whether it would be cost effective or even necessary.

Gonadotropins are also used to induce estrus in weaned sows that experience prolonged wean-to-estrus intervals. There is little experimental evidence supporting the use of gonadotropins for this purpose. However, is has been shown that injecting sows not in estrus by 7 days after weaning with gonadotropin did not improve their reproductive performance (Table 3).[18] These sows were probably infertile and gonadotropin treatment did not resolve this infertility.

Pharmacological treatments at breeding

A possible pharmacological intervention at breeding is the injection of oxytocin (5 IU intravulvally) at the time of AI. To perform an intravulval injection, we use a 20-g 0.5-inch needle and inject externally at the vulval-cutaneous junction. Research data have indicated that oxytocin

Table 3

Effect of PG600® on performance of sows with delayed (>7d) return-to-estrus

	Control	PG600®
Wean-service interval, days	16.8	14.6
Farrowing rate	66.9%	63.1%
Subsequent litter size	10.7	10.7

Adapted from Tubbs[18]

Table 4

Effect of inseminator experience and oxytocin on sow performance

Group (n=300 each)	Farrowing rate	Litter size (alive)
Inexperienced	77%	9.4
Inexperienced + oxytocin	89%	10.2
Experienced	86%	10.1
Experienced + oxytocin	91%	10.5

Adapted from Flowers[19]

treatment improved both farrowing rate and subsequent litter size (Table 4), especially for inexperienced technicians.[19]

In my clinical experience, I have observed a 5% increase in farrowing rate in two large start-up herds that received this intervention. However, these were not controlled studies. The use of oxytocin has been associated with adverse behavioral sow reactions (mild to extreme agitation) in 10%–15% of sows, reflecting the potency of this hormone and the likelihood of pain associated with its use. In contrast, the Alberta farms reported no adverse reactions. However, if adverse sow reactions are encountered, a low dose (25%–50%) of $PGF_{2\alpha}$ intravulvally should be substituted for the oxytocin, which should provide the same benefit.[20] The mechanism controlling this effect is not understood. However, since oxytocin will induce endogenous $PGF_{2\alpha}$ production (and vice versa), it is likely that both hormones will advance the onset of ovulation and so will result in a better synchronization between insemination and ovulation.

Controlling the time of parturition in sows

Before implementing an induction program, first confirm a viable reason for doing so:

- Do records indicate intervention levels for apparent stillbirths?
- Is induction to be employed in association with increased farrowing supervision?
- Is the turnaround time on farrowing crates such that long gestations must be avoided?

If farrowing is to be induced, do not use book values for gestation length; rather, determine gestation length on the individual farm and do not induce more than 2 days before the due date. Further, gestation must be periodically monitored, particularly in units with a high staff turnover. Calculate the gestation length from first breeding; depending on whether the sow is initially bred at the onset of estrus (and different personnel may differ in their subjective assessment of when estrus starts) or somewhat later, the breeding may vary by more than 24 hours relative to ovulation, resulting in an apparent change in mean duration of and/or increased variation in gestation length.

The ability to predictably induce farrowing will facilitate improved supervision and so reduce neonatal piglet mortality.[21] The administration of $PGF_{2\alpha}$ or its analogues has long been known to be effective for inducing parturition in sows,[22] but a considerable range in the interval between treatment and parturition can still be expected. Indeed, fewer than 65% of induced sows are likely to farrow during normal working hours and so be candidates for farrowing supervision.[21,23]

Various additional treatments have been applied in attempts to improve the promptness of parturition after $PGF_{2\alpha}$. The injection of oxytocin approximately 24 hours after the injection of $PGF_{2\alpha}$ has been shown to reduce the variation in the time to onset of parturition.[24] However, while oxytocin causes a more rapid and synchronous onset of parturition, it often disrupts the process of piglet delivery, necessitating manual assistance.[25–27] Injecting estradiol before or at the time of $PGF_{2\alpha}$ administration inconsistently affects the onset or duration of parturition.[28–30] The injection of carazolol, a β-andrenergic blocking agent, was shown in sows to result in a prompt onset of labor and an acceleration of the parturition process.[31,32] The mechanism whereby carazolol influenced farrowing has been suggested to involve the binding of myometrial β-andrenergic receptors, thereby inhibiting the tocolytic effect of endogenous epinephrine released in response to the pain of parturition.[32] Carazolol is not available in North America, so the Alberta Pork Research Centre is currently examining the potential benefits of other analgesics for the parturient process in sows.

It is now established that the intravulval injection of $PGF_{2\alpha}$ at half the manufacturer's recommended dose is as effective as an IM injection at the full recommended dose for inducting parturition in sows.[23,33] The reason for the efficacy of the lower $PGF_{2\alpha}$ dose administered intravulvally possibly involves a higher local ovarian $PGF_{2\alpha}$ concentration, since the venous drainage of the reproductive tract is greatly interconnected.[34] Therefore, an intravulval injection would likely result in a relatively high $PGF_{2\alpha}$ concentration in the uterine vein and thus, by countercurrent cycling, also in the ovarian artery. The Alberta Pork Research Centre is currently examining this hypothesis.

The forgoing discussion clearly indicates the efficacy of $PGF_{2\alpha}$ for inducing parturition in sows. However, the relative lack of predictability should also be addressed. It is known from work in sheep that terminal luteolysis requires a pulsatile release of $PGF_{2\alpha}$. Further, it has been shown that a poor response to $PGF_{2\alpha}$ is at least partially due to a failure to induce terminal luteolysis in some sows.[30] Assuming a similar requirement for pulsatile $PGF_{2\alpha}$ release in swine, a single $PGF_{2\alpha}$ injection may occasionally fail to initiate this pulsatile endogenous $PGF_{2\alpha}$ release. Therefore, if the luteolytic signal was reinforced, enhanced

Table 5

Influence of $PGF_{2\alpha}$ injection frequency and oxytocin on timing of farrowing in sows

	Interval from administration of $PGF_{2\alpha}$ to onset of farrowing				
	1 to 8 h	8 to 22 h	22 to 32 h	32 to 46 h	> 46 h
Experiment one					
Single $PGF_{2\alpha}$	3 (4.7%)	11 (17.2%)	36 (56.3%)	9 (14.1%)	3(4.7%)
Split dose $PGF_{2\alpha}$	2 (4.0%)	5 (10.0%)	42 (84.0%)	1 (2.0%)	0
$PGF_{2\alpha}$/oxytocin	3 (5.1%)	8 (13.5%)	47 (79.7%)	0	1 (1.7%)
Experiment two					
Single $PGF_{2\alpha}$	3 (7.0%)	11 (25.6%)	23 (53.5%)	3 (7.0%)	3 (7.0%)
$PGF_{2\alpha}$/oxytocin	10 (23.3%)	6 (14.0%)	26 (60.5%)	0	1 (2.3%)

predictability should ensue.

Exogenous oxytocin has been shown to cause an endogenous release of $PGF_{2\alpha}$ in sows in early gestation.[35,36] Further, a recent study has shown that 6 hours after an initial $PGF_{2\alpha}$ injection, a second $PGF_{2\alpha}$ injection or an injection of oxytocin markedly improved the predictability of parturition (Table 5).[37]

In the first study, oxytocin did not precipitate more farrowings during the first 24 hours, and so the effect was not comparable to the known effect on uterine contraction and piglet delivery of oxytocin given 20–24 hours after $PGF_{2\alpha}$ (i.e., stimulation of onset of piglet delivery). In a subsequent study, injection of oxytocin 6 hours after $PGF_{2\alpha}$ injection reduced the incidence of late-responding sows but also increased the number farrowing on the day of induction.[38] This indicates that the physiological response to oxytocin will depend on the proximity to natural onset of farrowing and, if natural farrowing is imminent, the uterine contraction/piglet delivery response may predominate. From these data, it would appear that the luteolytic signal (i.e., pulsatile $PGF_{2\alpha}$ release) can be reinforced by either more $PGF_{2\alpha}$ or more oxytocin. However, given the variable response to oxytocin, the split-dose $PGF_{2\alpha}$ should be recommended.

Experimental interventions

Included in this section are protocols that show promise but are still under investigation. They should not be attempted until more information is available.

Estrus synchronization

An alternative approach for estrus control and synchronization is to induce a prolonged luteal phase, and then induce luteolysis as required. To this end, ovulation and subsequent formation of corpora lutea will cause the production of progesterone, which will block estrus. If a prolonged luteal phase can be established, this progesterone production will be maintained until terminated by either a natural or induced luteolysis. A prolonged luteal phase can be established by the serial administration of estradiol between days 11 and 19 of the estrous cycle.[39] However, this is labor intensive and estradiol is not cleared for use in pigs. Another way to induce a prolonged luteal phase may be administering a single dose of human chorionic gonadotropin (hCG) on day 12 of the estrous cycle.[40] The mechanism involved is to induce follicular development and the endogenous production of estradiol.[40] Because this is a cleared product that is simple to use and inexpensive compared to other protocols, this approach is attractive.

The Alberta Pork Research Centre has recently examined applying hCG in this manner.[41] Forty-four PIC Camborough prepubertal gilts (86 kg [190 lb] bodyweight) were assigned either to receive

- an injection (IM) of 1000 IU hCG (Chorulon®, Intervet Canada) on day 12 of their estrous cycle (n=24), or
- no injection and serve as controls (n=20).

Boar exposure for estrus detection was implemented from day 15 until the end of the study and blood samples were obtained at 20 and 30 days for progesterone determination. Control gilts were allowed to cycle with no further intervention. Gilts receiving hCG and not showing estrus by day 30 received 175 cloprostenol (IM) to initiate luteolysis. Gilts returning between 17 and 24 days were considered to have had a cycle of normal duration. Gilts were slaughtered 5–10 days after their second estrus and their ovaries were recovered to determine ovulation rate.

Of the 20 control gilts, 16 had normal cycles, one had a short cycle (16 days), and three had long cycles (mean 30 days). Of the 24 hCG-treated gilts, one had a normal cycle, one had a short cycle (14 days), 15 had long cycles (mean 33 days), and seven were not detected in estrus and were considered to be the result of either estrus detection failure or failure of luteolysis. Of the 15 gilts exhibiting long cycles, two were detected as estrous on day 30 (day of $PGF_{2\alpha}$ injection), five were estrous on day 31, and one was estrous on day 32. Since the objective of the $PGF_{2\alpha}$ was to induce luteolysis and initiate the follicular phase, these extremely rapid responses suggest that natural luteolysis had already occurred. Therefore, while these data support the hypothesis that hCG administered at day 12 of the estrous cycle will effectively prolong the luteal phase, an extension of the estrous cycle beyond 28–30 days was not always realized. This contrasts with earlier data suggesting that a luteal phase of up to 60 days is possible when 1000 IU hCG was injected.[40] The earlier work further noted that the interestrus interval was dependent on the dose of hCG and it is possible that with modern pigs and/or the product employed, the 1000 IU dose we used

Table 6

Effect of GnRH at breeding on reproductive performance of gilts (mean ± SEM)

	GnRH	Control	*P*
Number of gilts	54	57	
Farrowing rate	88.9%	80.7%	.1
Litter size —total	10.4 ±0.3	8.9 ±0.4	.005
Litter size —alive	9.7 ±0.3	8.4 ±0.4	.007

was too low. We are currently examining this protocol further.

Numbers of corpora lutea tended to be higher (P=.14) in treated gilts (13.6±0.7 for controls and 15.2±0.7 for hCG-treated). This suggests that inducing a prolonged luteal phase may provide a benefit similar to skip-a-heat. However, the impact on subsequent fertility and fecundity requires further research. Therefore, this protocol should not be attempted until further information is available.

Another exogenous hormone that may provide benefit at the time of breeding is GnRH (Table 6).[42] At breeding at their second estrus, gilts received either

- an intramuscular (IM) injection of 150 µg GnRH (Fertagyl®; Intervet Canada; n=54), or
- no injections (controls).

Breedings were by a single AI at the detection of estrus with a minimum dose of 3×10^9 spermatozoa. GnRH injection increased both farrowing rate and litter size. The mechanism(s) involved in these effects are not clear but earlier work with GnRH-treated primiparous sows noted an increase in both circulating progesterone and numbers of embryos.[43]

Implications

- There are many opportunities to pharmacologically intervene in swine reproduction. However, it is the responsibility of the veterinarian to ensure that any intervention is warranted.
- Hormones and other pharmaceuticals are excellent tools in the management of swine herd reproduction, but their routine use should be avoided and they should never be allowed to substitute for good management practices.

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