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THE CONTROL OF OVULATION

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Extensive studies have been directed towards the effective control of oestrus and ovulation in the pig. Management procedures, including the simultaneous exposure of gilts to the boar or the weaning of pigs from a group of sows, have been developed for the synchronization of oestrus and ovulation in the pig herd. Other investigators have concentrated on the use of exogenous hormones or other compounds to interrupt the normal oestrous cycle as an additional approach toward oestrus and ovulation control.

The oestrous cycle may be altered by either suppressing ovarian activity to delay oestrus or by inducing premature regression of corpora lutea to hasten the onset of oestrus. Spontaneous follicular development usually occurs following these treatments in sexually mature animals. Regulation of luteal function or suppression of follicular growth will be referred to as *control of the luteal phase.* Precise control of the initiation of follicular development in anoestrous animals and of the occurrence of ovulation can be obtained by treatment with gonadotrophins. The use of exogenous hormones for this purpose will be discussed as *control of the follicular phase.* A review will be presented of reported studies that have used hormones and other compounds to control ovulation in the pig followed by results from recent investigations on the use of a synthetic progestagen, altrenogest, for the control of ovulation in pigs on commercial farms.

Control of the luteal phase

Progesterone and synthetic progestagens have been used to suppress the oestrous cycle. Daily injections of progesterone inhibits oestrus and, if adequate doses are given, results in normal fertility (Ulberg, Grummer and Casida, 1951; Baker *et al.*, 1954; Gerrits *et al.*, 1963). Likewise, several synthetic progestagens administered either orally or by injection have inhibited follicular growth and oestrus.

High doses of 6-methyl-17-acetoxyprogesterone (MAP) have been reported to inhibit oestrus without producing cystic follicles, but oestrus was usually not well synchronized and litter size was often reduced (Baker *et*

al., 1954; Dziuk, 1960, 1964; Nellor, 1960; Nellor *et al.*, 1961; Dziuk and Baker, 1962; First *et al.*, 1963; Dziuk and Polge, 1965). Oral administration of other progestational compounds including 6-chloro-Δ^6-17-acetoxyprogesterone (Wagner and Seerley, 1961; Veenhuizen *et al.*, 1965; Ray and Seerley, 1966), 17α-acetoxy-6-methylpregna-4,6-dien-3,20-dione (Pond *et al.*, 1965), or injections of norethandrolone (Martinat-Botte, 1975a) have produced results similar to those obtained with MAP. In general, the administration of progesterone or progestational compounds has not been a satisfactory treatment for controlling oestrus and ovulation because of the increased incidence of cystic follicles, decreased fertility at the first post-treatment oestrus and a lack of precise synchronization.

Two new progestagen compounds, SA-45249 (Mayer and Schutze, 1977a) and altrenogest (Webel, 1976, 1978; Davis *et al.*, 1980) offer a new opportunity for regulating the oestrous cycle. These compounds, when administered orally in sufficient doses, suppress oestrus and result in a synchronized return to oestrus following withdrawal, without a reduction in fertility or litter size. The two compounds are similar in structure and dosage requirements.

Low doses of 3 mg of SA-45249 (Mayer and Schutze, 1977a) or 2.5 mg of altrenogest (Webel, 1978; Redmer and Day, 1981) results in a high incidence of cystic follicles. Levels of 6 mg of SA-45249 or 10 mg of altrenogest are effective for oestrus synchronization with a low incidence of cystic follicles. Recommended doses for general use of altrenogest are 15–20 mg which effectively synchronizes oestrus with minimal numbers of cystic follicles (Webel, 1978; Redmer *et al.*, 1979; Davis *et al.*, 1980; Kraeling *et al.*, 1981). Treatment durations of 10–18 days were investigated with the longer durations producing shorter intervals to oestrus and closer synchronization of oestrus after withdrawal (Schutze and Mayer, 1977; Webel, 1978). A minimal 14-day feeding period appears to be necessary to control oestrus in gilts at all phases of the oestrous cycle when treatment is initiated (Stevenson and Davis, 1981). As expected, individual feeding where each animal receives the prescribed dose produces closer synchronization of oestrus than group feeding (Zerobin, 1977; Martinat-Botte *et al.*, 1980).

The study of endogenous hormones associated with SA-45249 (Mayer and Schutze, 1977b) or altrenogest (Redmer and Day, 1981) suggest that both compounds work in a similar manner by inhibiting follicular growth. There is no influence on the lifespan of the corpus luteum.

Effective control of the oestrous cycle has been obtained by inhibiting ovarian function with a non-steroidal compound, ICI 33828 (a dithiocarbamoylhydrazine derivative). A high proportion of sows or gilts exhibited oestrus 5–8 days after withdrawal of the compound following an 18–20-day feeding period and fertility was not reduced following treatment with this compound (Polge, 1965, 1966; Gerrits and Johnson, 1965; Stratman and First, 1965; Groves, 1967; Polge, Day and Groves, 1968). Use of ICI 33828 was curtailed and regulatory approvals withdrawn in many countries following reports of teratogenic effects in pregnant gilts.

Another method for regulating the oestrous cycle is to induce accessory corpora lutea in cycling animals and then allow them to regress normally. Injections of pregnant mare's serum gonadotrophin (PMSG) followed by

human chorionic gonadotrophin (HCG) induces ovulation at any stage of the oestrous cycle. The accessory corpora lutea then regress after an approximately normal life span with oestrus occurring 18–24 days after the HCG injection (Neill and Day, 1964; Day *et al.*, 1965; Caldwell *et al.*, 1969). Although this treatment offers some degree of oestrus synchronization, it is not very precise because of the variability in the duration of luteal function and the early regression of accessory corpora lutea induced during the first six days of the cycle.

Interruption of the oestrous cycle by shortening the life span of the corpus luteum is another method of oestrous cycle control. The injection of oestrogen in the pig often has luteotropic effects (Gardner, First and Casida, 1963; Dziuk, 1964) as contrasted to the luteolytic influence in the cow. It is not, therefore, an effective treatment for reducing the length of the oestrous cycle. Prostaglandins are not luteolytic in the pig until about day 11 or 12 of the cycle, so they also do not offer a practical means of synchronizing oestrus (Diehl and Day, 1974; Hallford *et al.*, 1975; Guthrie and Polge, 1976a; Lindloff *et al.*, 1976). However, effective synchronization has been obtained when prostaglandins were used to regress corpora lutea during pregnancy (Guthrie, 1975; Guthrie and Polge, 1976b), or following oestrogen treatments to prolong luteal function (Guthrie, 1975; Guthrie and Polge, 1976b; Kraeling and Rampacek, 1977). Regression of accessory corpora induced by gonadotrophins has also been reported by Guthrie (1979) to provide a means for the control of oestrus.

Control of follicular phase

Pituitary gonadotrophic preparations, pregnant mare serum gonadotrophin (PMSG), human chorionic gonadotrophin (HCG), hypothalamic releasing hormones (GnRH), or combinations of these hormones have been widely used to induce follicular growth or ovulation. These treatments have been used in prepubertal gilts, during the luteal and follicular phase of the oestrous cycle, in anoestrous gilts or sows, in lactating or early weaned sows and following suppression of the oestrous cycle with other exogenous hormones.

As early as 1935, Casida demonstrated that ovulation could be induced in prepubertal gilts by giving multiple injections of PMSG or purified pituitary preparations. These observations were confirmed by du Mesnil du Buisson (1954), Dziuk and Gehlbach (1966) and Baker and Coggins (1968). Although injection of PMSG followed by HCG 48–96 hours later induced a fertile ovulation, pregnancy was not usually associated with such a treatment in gilts 4–5 months of age unless exogenous progestagens or gonadotrophins were given after breeding, as the corpora lutea normally regressed by day 20–25 of pregnancy (Shaw, McDonald and Baker, 1971; Segal and Baker, 1973; Ellicott, Dziuk and Polge, 1973; Rampacek *et al.*, 1976). Other workers using a combination of PMSG and HCG given as a single injection have reported synchronized oestrus and ovulation in prepubertal gilts (Schilling and Cerne, 1972; Baker and Rajamahendran, 1973; Guthrie, 1977). The sometimes conflicting results on pregnancy rates

in the prepubertal pig need further clarification regarding such variables as breed, age, dose and combinations of hormones.

It has also been well established that superovulation can be induced in pigs by the injection of appropriate gonadotrophins (Tanabe *et al.*, 1949; Gibson *et al.*, 1963; Hunter, 1964, 1966; Longenecker, Lasley and Day, 1965; Day *et al.*, 1967; Longenecker and Day, 1968; Phillipo, 1968; Christenson *et al.*, 1973). However, litter size at farrowing has not consistently been increased and may only be significantly increased by PMSG in sows which have lower than average litter sizes when untreated (Schilling and Cerne, 1972).

The time of ovulation can be precisely controlled by the injection of HCG (Dziuk and Baker, 1962; Dziuk, Polge and Rowson, 1964; Hunter, 1964, 1966; Buttle and Hancock, 1967), or GnRH (Baker, Downey and Brinkley, 1973; Webel and Rippel, 1975; Guthrie, 1977; Guthrie, Pursel and Frobish, 1978) 48–96 hours after PMSG. Attempts to induce follicular stimulation, superovulation or oestrus with gonadotrophin-releasing hormone have apparently been unsuccessful (Baker and Downey, 1975; Guthrie, 1977; Webel, 1978). However, recent unpublished work in the author's laboratories suggest that whereas a single injection of large doses of GnRH is ineffective, frequent repeated injections of small doses promote follicular growth and development. J.H. Britt (personal communication) reported induction of oestrus and ovulation in lactating sows injected with 2.5 μg GnRH every two hours for seven days. More data will be needed, however, before practical application can be recommended.

The ability of PMSG to stimulate follicular development and of HCG to control precisely the time of ovulation has been utilized to synchronize ovulation and to allow insemination at a fixed time. This combined treatment (PMSG + HCG) has been used following inhibition or suppression of the oestrous cycle with compounds such as ICI 33828 (Polge, Day and Groves, 1968; Webel, Peters and Anderson, 1970; Christenson *et al.*, 1973; Baker, Shaw and Dodds, 1970) or following oral administration of progestagens (Dziuk and Baker, 1962; Dziuk and Polge, 1965). The sequence of treatments (ICI 33828/progestagen + PMSG + HCG) is effective for either controlling the time of ovulation to allow a single insemination or to induce superovulation. Other uses of PMSG and HCG have been to synchronize oestrus in sows by injecting PMSG on the day of weaning to shorten the interval to the first oestrus, or the injection of PMSG followed by HCG 80–96 hours later in order to synchronize ovulation and permit a single insemination (Longenecker and Day, 1968; Christenson and Teague, 1975; Soma and Speer, 1975).

In recent years, an increasing number of farms have placed the breeding herd in controlled-environment, limited-space housing. Several reproductive problems have been associated with these confined conditions including delayed puberty in gilts, and the failure of sows to return to oestrus following weaning, particularly in the late summer. Injection of PMSG or a combination of PMSG/HCG as a single injection to sows at weaning or to non-cycling gilts has overcome these anoestrous problems and shortened the time of oestrus (Dziuk and Dhindsa, 1969; Schilling and Cerne, 1972; Hurtgen, 1976; Hurtgen and Leman, 1979).

The use of gonadotrophins to induce ovulation during lactation has

recently attracted renewed attention. Pregnancy has been induced in lactating animals but with quite variable results, especially when administered soon after parturition. The ovarian response to PMSG was increased as the interval from parturition to injection increased, but consistently good results were not obtained (Heitman and Cole, 1956; Epstein and Kadmon, 1969; Crighton, 1970a, 1970b; Martinat-Botte, 1975b; Hausler *et al.*, 1980). Follicular development may occur without ovulation when sows are given only PMSG (Martinat-Botte, 1975b; Guthrie, Pursel and Frobish, 1976, 1978; Webel, unpublished). Normal fertility has been obtained in lactating sows with an injection of PMSG at 25 days post-partum followed 96 hours later by HCG (Kuo, Hodson and Hausler, 1976; Hausler *et al.*, 1980). The injection of a follicle stimulant such as PMSG or PMSG/HCG combination followed by HCG or GnRH to induce ovulation seems to offer a possible means for inducing pregnancy in the lactating sow. However, questions regarding the breed of sow, the stage post-partum and the doses of the hormones must be answered before a management system can be widely recommended.

Use of altrenogest for reproductive management in gilts

Altrenogest may be a useful tool in the management of the breeding herd because of its effectiveness for regulating and synchronizing the oestrous cycle. Altrenogest (17α-allyl-estratiene-4-9-11, 17-β-ol-3-one) is a synthetic steroid with progestagenic activity. This compound was previously identified as allyl trenbolone and is also identified by the numbers A-35957 and RU-2267. The proprietary name is REGU-MATE®. Altrenogest is a product of Roussel-Uclaf and is being developed for use in synchronizing oestrus in gilts and sows. This synchronization permits planned breeding within a preplanned period of 3–5 days and facilitates introduction of gilts into the breeding herd. Oestrus in weaned sows and gilts can be scheduled to occur simultaneously by coordinating the dates for weaning sows and feeding altrenogest to gilts. Oestrus synchronization is obtained by feeding the compound for 18 days at levels of 15 or 20 mg/gilt/day.

The effectiveness of altrenogest for synchronizing oestrus in gilts which have exhibited at least one previous oestrus is illustrated by two histograms in *Figure 10.1.* Up to 100% of treated gilts have expressed oestrus within a 3-day period (Mauleon, Martinat-Botte and Scheid, 1979) and in some individual trials with small numbers of gilts, all gilts were in oestrus on a single day (Webel, unpublished). However, these histograms depict more typical results observed with larger numbers of gilts. Pursel *et al.* (1981) observed 80% of the treated gilts in oestrus within a two-day period and 97% within four days. In trials on French farms 65% of the gilts were in oestrus on days 6 and 7 and 93% in oestrus on days 5–8 (A. Jobard, J.M. Boisson and J.P. Scheid, personal communication). In the study reported by Pursel *et al.* (1981), all gilts were fed 15 mg daily on a single farm, whereas the French trial was conducted on different farms with a daily dose of 20 mg. These variations in the trials may explain the difference in precision of synchronization since a more consistent response would be expected in a single herd. Also, the increase in interval and oestrus

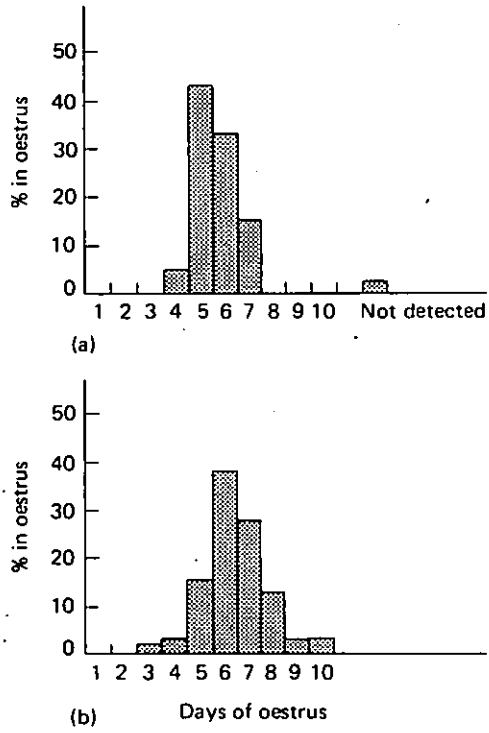

Figure 10.1 Oestrus synchronization following altrenogest in gilts with a previous oestrous cycle recorded. (a) Dosage: 15 mg/gilt/day; n = 60. By courtesy of Pursel *et al.* (1981). (b) Dosage: 20 mg/gilt/day; n = 175. By courtesy of Jobard *et al.* (unpublished)

following the higher dose is consistent with earlier studies (Webel, 1978, 1980; Kraeling *et al.*, 1981).

Fertility at the first oestrus following synchronization with altrenogest has not been different from controls; however, there has been a tendency for an increase in ovulation rate and litter size in treated gilts (Webel, 1978; Davis *et al.*, 1980). A summary of reported farrowing rates and litter sizes is shown in *Table 10.1*. Increased litter sizes have not been consistently

Table 10.1 FERTILITY FOLLOWING SYNCHRONIZATION OF OESTRUS WITH ALTRENOGEST IN SEXUALLY MATURE GILTS

Treatment	*Number of animals bred*	*Percent farrowed*	*Litter size*	*Reference*
Control	145	83	10.0	Jobard *et al.*, unpublished
Altrenogest (20 mg)	175	83	10.7	
Control	70	60	10.0	Webel, 1978
Altrenogest (15 mg)	68	75	11.3[a]	
Control	68	74	9.1	Pursel *et al.*, 1981
Altrenogest (15 mg)	58	71	10.5	
Control	29	86	9.8	Britt, 1980
Altrenogest (15 mg)	48	85	9.9	

[a]Significantly (P<0.05) different from control group.

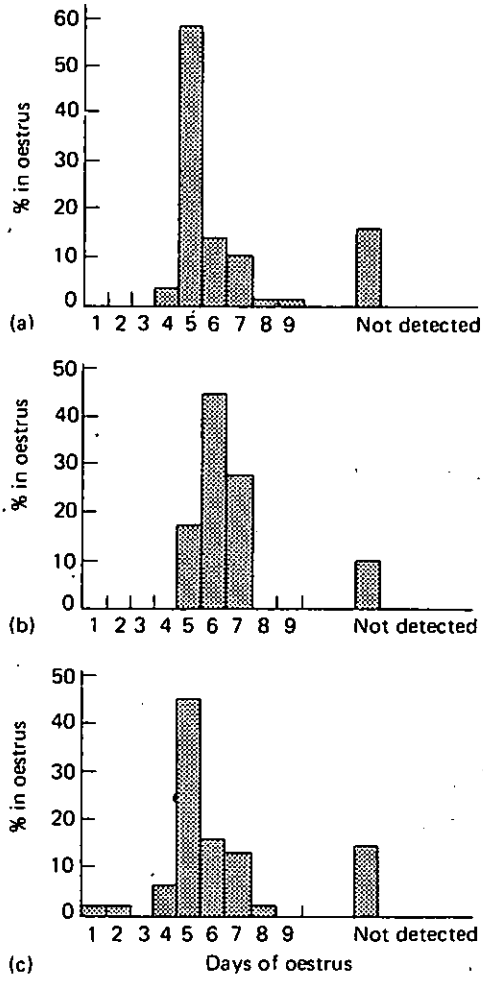

Figure 10.2 Oestrus synchronization following altrenogest in gilts on commercial pig farms without previous records of oestrous cycles. (a) Dosage: 15 mg/gilt/day; n = 175. (b) Dosage: 15 mg/gilt/day; n = 29. (c) Dosage: 15 mg/gilt/day; n = 62

observed in all trials, but in some cases the difference has been statistically significant.

In contrast to controlled research studies, previous oestrous records are seldom available on commercial pig breeding farms, and in many cases the gilts have not reached puberty or are in a state of anoestrus. If only gilts with a previous record of oestrus are used, the synchronization results on commercial farms following altrenogest are similar to those shown in *Figure 10.1.* However, most trials have been conducted on farms where the previous history was not available. A summary of results from these farms is shown in *Figure 10.2.* Although the precision of synchronization for those gilts that exhibited oestrus was similar to previous observations, 10–15% of the gilts were not observed in oestrus following treatment. These gilts were similar in age (7–9 months) to those used in the studies

shown in *Figure 10.1*, but may not have exhibited a previous oestrus. These results agree with other reports (O'Reilly *et al.*, 1979; Webel, Scheid and Bouffault, 1980) where 65–75% of those gilts in which previous records of oestrus behaviour were not known exhibited a synchronized oestrus.

In a trial at the University of Missouri, 12 of 49 gilts allotted to altrenogest had not been observed in oestrus. Seven of these (58%) were synchronized following treatment compared with 78% of those which had shown oestrus previously. These results provide evidence that a lower proportion of non-cycling animals are synchronized compared with gilts that had been detected in oestrus prior to treatment. In other studies the ovaries of gilts which did not exhibit oestrus following withdrawal of altrenogest were examined. In many cases these gilts had inactive ovaries indicating that they were not cycling or had not yet attained puberty (Webel, 1978; Britt, 1980; Martinat-Botte *et al.*, 1980). These reports are consistent with the observations that altrenogest effectively synchronizes oestrus in cycling gilts with active ovaries but is less effective in inactive gilts. On commercial farms a similar proportion of animals treated with altrenogest have been observed in oestrus within a 4-day period as compared with a 25-day period for controls. When the proportion of controls which expressed oestrus within 25 days was low the proportion of gilts synchronized following altrenogest was also low. In contrast, if a high proportion of controls were in oestrus a high proportion of treated gilts were effectively synchronized. This proportion varies from about 50% up to 100%, averaging around 85%. In general, approximately 95% of those gilts which had exhibited a previous oestrus were synchronized to a 4-day period whereas only about 75–85% of similar gilts whose reproductive history was not known were synchronized.

The farrowing rate and litter size for three farms are shown in *Table 10.2*. The lower farrowing rate for controls differs from previous observations in controlled laboratory trials. Although there is no clear explanation for these differences the close synchronization of oestrus in treated gilts may facilitate management. Perhaps the breeder took greater care when

Table 10.2 FERTILITY FOLLOWING ALTRENOGEST SYNCHRONIZATION ON COMMERCIAL PIG BREEDING FARMS

Treatment	*Number of animals bred*	*Percent farrowed*	*Mean litter size*
Trial 1			
Control	43	30[a]	9.3
Altrenogest (15 mg)	53	58[b]	10.9
Altrenogest (20 mg)	54	52[b]	11.0
Trial 2			
Control	26	54[a]	9.8
Altrenogest (15 mg)	26	78[b]	9.2
Altrenogest (20 mg)	26	85[b]	10.7
Trial 3			
Control	25	40	10.7
Altrenogest (15 mg)	25	68	9.4
Altrenogest (20 mg)	23	57	10.3

[a],[b]Means within trials with different superscripts are significantly different ($P<0.05$).

breeding synchronized gilts for 3–5 days than when breeding controls during a 3-week period.

The effectiveness of altrenogest in young gilts that had not been observed in oestrus was evaluated on a farm where gilts were bred at approximately 6 months of age rather than at 8–9 months. Gilts were selected at approximately 100 kg body weight and moved from the growing/finishing building to the breeding building on a Friday or Saturday and altrenogest feeding began on the following Monday. The probability that these gilts had exhibited a previous oestrus was low. Controls were handled in a similar manner. The cumulative percentages in oestrus by day 10, 20, 30 and 40 are shown in *Table 10.3*. These calculations are based on

Table 10.3 OESTROUS RESPONSE FOLLOWING ALTRENOGEST IN THE YOUNG GILT

Observation	*Control*	*Altrenogest*	
		7 days	*14 days*
Number of gilts	26	28	36
Cumulative percent in oestrus by day:			
10	15[a]	57[b]	61[b]
20	23[a]	64[b]	67[b]
30	27[a]	64[b]	67[b]
40	54[c]	68[d]	72[d]

Days to oestrus were calculated from the last day fed for altrenogest or from the date moved to the breeding area for controls.
[a],[b]Numbers in rows with different superscripts are different ($P<0.05$).
[c],[d]Numbers in rows with different superscripts are different ($P<0.10$).

the number of days following the last altrenogest administration for treated gilts and from the date moved to the breeding area for controls. A higher proportion ($P<0.10$) of treated animals were in oestrus at each time period. To compare the total number of days from selection to oestrus, one must add 7 or 14 days to the treated animals to compensate for the feeding period. However, even when the proportion of controls in oestrus by 30 days (27%) is compared with the percentage of treated gilts in oestrus by 10 days (57% and 61%), an advantage still exists for gilts fed altrenogest. In fact, there was a similar proportion in oestrus within 10 days post-treatment (57% and 61%) as within 40 days (54%) in controls. Altrenogest appeared to promote an earlier and more synchronized attainment of puberty in these gilts.

Even though the proportion of young gilts exhibiting a synchronized oestrus (57% or 61%) was lower than observed in older gilts in farm trials (*Figure 10.2*; approximately 85%) or in cycling gilts (*Figure 10.1*; 95% to 100%), treatment of young gilts with altrenogest would appear to provide a useful management tool to the pig producer.

Christenson and Ford(1979) have found that depending on the breed and confinement conditions, between 52% and 94% of gilts tested with boars from 145 days of age had exhibited regular oestrous cycles by 9 months of age. Therefore, altrenogest may be a tool for selecting gilts that will show puberty at an early age and eliminate the need to maintain large numbers of gilts for several months before introduction into the breeding herd.

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