PROSTAGLANDINS
IN
ANIMAL REPRODUCTION

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EDITED BY

LARS-ERIC EDQVIST
Department of Clinical Chemistry, College of Veterinary Medicine,
Swedish University of Agricultural Sciences,
S-750 07 Uppsala, Sweden

and

HANS KINDAHL
Department of Obstetrics & Gynecology, College of Veterinary Medicine,
Swedish University of Agricultural Sciences,
S-750 07 Uppsala, Sweden

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PRACTICAL USES OF PROSTAGLANDINS IN PIGS

By
M. J. Bosc, F. Martinet-Botte, M. Terqu

ABSTRACT

In pigs, most of the studies have emphasized the roles of prostaglandins and specially of PGF2α during the oestrous cycle, at the time of implantation and at the end of gestation. As they are involved in the stages of reproduction which concern the organization and productivity of the breeding, applications have then been proposed and used to control oestrus and ovulation, to make an early pregnancy diagnosis, and mostly to induce and synchronize parturition.

prostaglandins, pigs, oestrous cycle, pregnancy diagnosis, parturition.

When one discusses the practical applications of prostaglandins in pig breeding, one can deal with every stage of reproduction which concerns the organization and productivity of the breeding. In fact, with pigs as with other mammalian species, prostaglandins are involved in most of the processes of reproduction, and their effects have been subject of many reports, the majority of which have dealt with the luteal function during oestrous cycle and gestation. Here we only propose to present the main applications which have been suggested for and developed with the prostaglandin F2α (PGF2α) or their synthetic analogues (APGF).

Control of oestrus and ovulation

In the sow, there are relatively few occasions to use prostaglandins or their analogues to control oestrus and ovulation because they are in fact employed for their luteolytic properties. At the end of lactation, and with prepuberal sows, the problem is to induce and to group the oestrus and ovulation in animals which have not had a preceding oestrous cycle. Different techniques have then been proposed based on use of gonadotropin hormones too. On cyclic animals, prostaglandins can only be used to control the length of the luteal phase and therefore the secretion of gonadotropin hormones.
Figure 1. Evolution in the peripheral blood of the 13,14-dihydro-15-keto PGF\(_{2\alpha}\) (PGFM) in cyclic and pregnant sows (55).

In the cyclic sow, corpora lutea (CL) which form after ovulation, secrete progesterone during the luteal phase which lasts about 14-15 days. The evolution of the levels of progesterone in the blood have been well established (21, 22, 41, 56, 70, 76), and circulating levels can reach 40 to 50 ng/ml. At the end of the luteal phase, it drops drastically and that drop is preceded by an increase of blood levels of PGF\(_{2\alpha}\) (50, 59, 61) or of 13,14-dihydro-15-keto-PGF\(_{2\alpha}\) (PGFM) (55) (Fig. 1), the secretions of which probably oscillate characteristics in the uterine-ovarian-venous blood. This chronology of secretion has suggested that PGF\(_{2\alpha}\) was the luteolytic agent of the sow oestrous cycle. In the sow as in other mammals, hysterectomy leads to prolongation of the life of CL (57). Moreover, at the beginning of gestation, the levels of PGF\(_{2\alpha}\).
in uterine venous blood or of PGFM in peripheral blood (55) are much lower than during the oestrous cycle (Fig. 1) even though large quantities of PGF_{2\alpha} or of PGFM can be measured in uterine flushings (28). Hysterectomy or embryos which both prevent the regression of CL therefore inhibit the endocrine secretion of PGF_{2\alpha} (3), this effect, at the beginning of gestation, has been attributed to secretion of oestrogens by the embryos (3). In the sow, however, the effects of a single administration of PGF_{2\alpha} differ according to the age of the CL. In fact, they do not regress if PGF_{2\alpha} is given before the 12th day of the cycle, after that time PGF_{2\alpha} (12, 14, 17, 37, 53) or its analogue (34) induce luteolysis and sows come into oestrus again a few days after. This happens also after hysterectomy (60).

As this luteolytic effect of PGF_{2\alpha} and of its analogue is related to the development of corpora lutea, the period during which PGF_{2\alpha} can be employed for synchronizing oestrus is too short to be useful in contrast to the bovine species (13, 50, 75). Several solutions have been suggested to get around that difficulty, they have been based on the prolongation of the luteal phase. The first utilizes oestrogens since their administration between the 10th and the 14th day of the cycle prolongs the luteal phase (10, 29, 48, 58). PGF_{2\alpha} then exercises a luteolytic effect when it is administered at least five days after the oestrogens (33, 48). The second is based on induction of new CL by injection of exogenous gonadotropins. The CL induced in this way after the 8th day of the cycle prolong its length by five to fifteen more days (8, 65), luteolysis can be obtained by PGF_{2\alpha} analogue when CL are sensitive to the luteolytic action of PGF_{2\alpha} (34) (Table 1). The third solution results from the fact that secretion of progestosterone is maintained during pregnancy (32, 56, 76) and that administration of PGF_{2\alpha} or their analogues leads to abortion followed by oestrus and ovulation (14, 36, 45, 49) (Table 1). The fourth and final solution which has been proposed is to associate PGF_{2\alpha} or one of its analogues with a short progestagen-treatment (54) as has been done with cows (75). In this case for groupying oestrus a luteolytic agent should be given to obtain the regression of CL of those animals for which the progestagen treatment was started at the beginning of the cycle. Table 1 presents the different methods which have been suggested for the sow in regard to the use of PGF_{2\alpha} or PGF_{2\alpha} analogues for the control of oestrus and ovulation. The consequences of all these treatments on fertility and prolificacy are good as has also been shown by trials carried on gilts regardless of the stage of their cycle (53) The shortest technique is the combination of progestagen and PGF_{2\alpha} analogue which can be used at any stage of the oestrous cycle. The treatments using exogenous gonadotropins or oestrogens appear more complicated to use
<table>
<thead>
<tr>
<th>References</th>
<th>Physiological Status</th>
<th>Treatment with PMSG or with an analogue</th>
<th>Oestrus synchronized treated animals</th>
<th>Pregnant inermated</th>
<th>Prolicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guthrie (33)</td>
<td>cycle 8E from day 10 to 14</td>
<td>-</td>
<td>1/4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guthrie and (x)</td>
<td>cycle 12 days after HCG</td>
<td>1/2</td>
<td>11/22</td>
<td>19/29</td>
<td>24/30 (80%) 11.8</td>
</tr>
<tr>
<td>Polge (35)</td>
<td>cycle Androgen 9 days from day 1 to 5 at the end of androgen</td>
<td>no PGF</td>
<td>7/20 (20%)</td>
<td>15/18 (75%)</td>
<td>15/20 (10.2)</td>
</tr>
<tr>
<td>Martin-Botte et al. (54)</td>
<td>cycle Androgen 9 days from day 6 to 10 at the end of androgen</td>
<td>no PGF</td>
<td>9/7 (85.7%)</td>
<td>8/10 (80.2%)</td>
<td>10/12 (10.9)</td>
</tr>
<tr>
<td>Guthrie and (x)</td>
<td>gestation day 12</td>
<td>-</td>
<td>8/12</td>
<td>11/12</td>
<td>17/12</td>
</tr>
<tr>
<td>Polge (36)</td>
<td>day 20</td>
<td>-</td>
<td>11/12</td>
<td>10/12</td>
<td>12/6 (86.7) 44/52 (84.6%) 12.4</td>
</tr>
</tbody>
</table>

PGF₂α has been used at doses of 10 mg. (x) PGF₂α analogues. EB Estradiol Benzoate (5 or 10 mg). PMSG: Pregnant Mare Serum Gonadotropin - HCG. Human Serum Gonadotropin. * Prolificity at autopsy 4-8 days or 25-30 days after insemination. ** Prolificity at 30 days of pregnancy. Androgen: Norethandrolone 9 injections (30 mg/day).
and they are longer than the preceding ones. The treatments done after the 12th day of gestation are effective and easy to realize, but will breeders be willing to make their animals abort in order to inseminate them again? 

Early diagnosis of gestation

In the sow, large quantities of PGF2α (30, 59, 61) and of PGFM (55) (Fig. 1) are secreted in the uterine ovarian venous blood between the 13th and the 16th day of the cycle, while these plasmatic levels are much lower at the comparable time during pregnancy (55, 61) (Fig. 1). The difference between these two physiological states can theoretically be used to make a diagnosis of gestation as has already been done with the plasmatic progesterone (74). This possibility has recently been tested with blood samples collected 13 to 15 days after insemination. One of the problems of this technique is the conservation of the blood sample during the 24 to 48 h needed to transport it to the laboratory. To examine this problem, each sample (collected on indomethacin and heparin) was divided in two parts. The first was centrifuged and quickly frozen, the second was mailed to the laboratory where it received the same treatments. Analysis was then made according to the technique of Kindahl et al. (46) and by separating the free and bound fractions by immunoprecipitation with a second antibody. The comparison between the two parts has shown that 99% of them were identical. The results of this diagnosis of gestation are presented in Table 2. The accuracy is 90% for pregnant sows and 68% for nonpregnant, the accuracy varies slightly depending on the moment of sampling, the 14th day after insemination being the most favourable. It may be noted that the accuracy for the nonpregnant animals is better when they return to oestrus 18 to 25 days after insemination. This technique also detects 68% of the sows which come back into heat later or which manifest a longer oestrus. For a fertility of 60 or 80%, the total accuracy is between 80 and 97%, which is slightly lower than the accuracy obtained by a good oestrus detection (66). Given further improvements, the results could probably be improved and this technique made more attractive.

Control of farrowing time

It is usually thought that the length of gestation of the sow varies little as compared with other species. Births are however spread over a week, most occurring between the 111th and the 117th day of gestation. Moreover, they can occur at any time of the day, even though there are marked circadian rhythms of parturition (68). These rhythms vary according to environmental conditions (68), but do not seem to change with length of gestation (7). Parturition in the sow is the result of changes of uterine motility which develop
Table 2. Accuracy of a pregnancy diagnosis based on the plasmatic levels of PGF$_{2\alpha}$ metabolite in the sow.

<table>
<thead>
<tr>
<th>Days of sampling (post-insemination)</th>
<th>13th</th>
<th>14th</th>
<th>15th</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>Pregnant sows (n.)</td>
<td>96</td>
<td>101</td>
<td>95</td>
<td>292</td>
</tr>
<tr>
<td>accuracy (%)</td>
<td>94</td>
<td>90</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>Non-pregnant sows</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with oestrus 18.25 days (n.)</td>
<td>25</td>
<td>21</td>
<td>12</td>
<td>58</td>
</tr>
<tr>
<td>(after insemination)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>accuracy (%)</td>
<td>68</td>
<td>81</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>with delayed oestrus (n.)</td>
<td>21</td>
<td>13</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td>(after insemination)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>accuracy (%)</td>
<td>57</td>
<td>62</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>total non-pregnant (n.)</td>
<td>46</td>
<td>34</td>
<td>17</td>
<td>97</td>
</tr>
<tr>
<td>accuracy (%)</td>
<td>63</td>
<td>74</td>
<td>71</td>
<td>68</td>
</tr>
</tbody>
</table>

Fertility = 0.6  Total accuracy (%) 81.60 83.60 80.60 81.20

Accuracy = % of correct diagnosis in the total diagnosis realized.

10 to 20 h before the completion of gestation (73, 80). The expulsion phase of piglets lasts on the average 2 to 3 h and it is characterized by its variability (5). These uterine changes are related to an abrupt drop of the level of progesterone in the maternal blood (73), they are preceded by numerous modifications of hormonal secretions in both the maternal and fetal blood (26, 27, 69). According to Nara and First (63) the sudden drop of the maternal level of progesterone occurs in response to an initial increase in the level of PGF$_{2\alpha}$-PGF$_{2\alpha}$ and PGFM then increase rapidly in the maternal blood (63, 69). The fetal blood and the amniotic fluid (69), these increased levels in the maternal side apparently stimulate the secretion of oxytocin (26) further encouraging uterine contractions (25, 67). In the sow, the production of progesterone by CL is responsible for maintaining gestation (27), and the means for controlling the moment of parturition are therefore related to the artificial maintenance or suppression of the level of progesterone in the blood. There
is no advantage in prolonging gestation because prenatal losses are considerably increased (27). The most elegant solution is to induce parturition before it would happen naturally by an appropriate luteolytic mechanism. PGF$_{2\alpha}$ is apparently responsible for luteolysis at the end of gestation in sows. Nara and Furst (63) have observed an increase of PGFM in the maternal blood at the time when the progesterone level dropped. The use of indomethacin which inhibits the synthesis of PGF$_{2\alpha}$ prevents this increase in the plasma, and luteolysis is restored by exogenous PGF$_{2\alpha}$ (63). In addition, numerous studies have shown that exogenous PGF$_{2\alpha}$ induces luteolysis at the end of gestation (11, 15, 31, 45, 78) as well as their analogues (42, 44) without modifying the evolution of plasmatic oestrogens (31, 42), although Wetterman et al. (78) have reported lower levels among the treated animals compared with the controls. The factors which control the luteolytic mechanism that determine the end of gestation in the sow are not well understood. We know that they depend on the fetuses (4, 71) and that they involve corticosteroids and indirectly the secretion of PGF$_{2\alpha}$ (64).

The induction of parturition in sows can therefore theoretically be realized in several ways. The use of synthetic corticosteroids in large doses leads to reduction of the length of gestation but its variability is as great as in the controls (27, 47). The administration of oxytocin is only effective a few hours before expulsion (62), and the use of other compounds known to stimulate the smooth muscle (acetylcholine, pilocarpine or serotonin) has no effect (20). The only effective technique is to use the luteolytic properties of prostaglandins and the tests done with PGF$_{2\alpha}$ or their analogues have demonstrated all the possibilities they offer (27, 43, 51). After a single or repeated injections of PGF$_{2\alpha}$ or one of their analogues, 90 to 95% of the sows give birth within a period of 48 h, and there are very few failures. In our trials with a PGF$_{2\alpha}$ analogue, cloprostenol, 80% of the sows farrowed between the 18th and the 36th h after administration, only 6.3% during the working hours of the day after the treatment. The synchronization of births varies somewhat according to different studies (9, 19, 22, 38, 39, 77). The degree of grouping is possibly influenced by the specific circadian rhythms of each breed. The average intervals 'treatment-parturition' which have been reported to vary between 20 to 40 h (Fig. 2) depending on the stage of gestation are not correlated with litter size (6). Their variability is generally less than 10 h and seems independent of the stage of gestation at which the treatment is given (Fig. 2).

The induced parturitions apparently take place normally. The expulsion of the piglets and the placentas are the same as in the controls (16, 27, 42, 77). The survival of the piglets at birth seems unaffected by the induction of parturition (Fig. 3). When the supervision of the sows is well organized, post-
Figure 2. Interval 'Treatment-Parturition' with a PGF₂α analogue (cloprostenol) according to the day of its administration. Data of successive trials in four different breeds (○: breed I, ●: breed II, ▲: breed III, ●: breed IV; *: the sows have received (i.m.) 15 mg of estradiol benzoate on the three days preceding parturition).
Figure 3. Survival rates of piglets after induction of parturition at different stages of pregnancy with a PGF$_2$ analogue (cloprostenol). Data from three trials (I-III) (c) control sows, the treated sows farrowed at days 109, 111 and 113 of pregnancy.

Natal losses can be reduced in particular by limiting the proportion of live-born piglets crushed by their mothers (2, 9, 19, 77). However, when birth is induced too prematurely (more than 3 days) post-natal survival is reduced (19, 38, 79), most losses occurring during the first three days of lactation (Fig. 3). The birth weight and growth of the piglets born after the treatment is on the average slightly below that of the controls (1, 6, 19, 72, 79). The growth rate during the first week of lactation seems to depend on their degree of prematurity (Girault & Bosc, preliminary results). In order to determine if prematurity of the piglets or lactation was responsible for this effect on growth, half a litter of a sow treated at day 108 of pregnancy was given at
Figure 4. Growth of premature (P.P.) or control (C.P.) piglets put at birth under a prostaglandin treated (I.S.) or a control (C.S.) sow. The treated sows have farrowed on day 109 of pregnancy after induction with a PGF2α analogue (cloprostenol) (9 pairs of sows).

Birth to a control sow and reciprocally half a litter of the control sow was placed under the treated one. Nine pairs of sows were utilized and the growth of the piglets measured up to weaning. This experiment has shown (Fig. 4) that premature piglets have the same growth rate regardless of whether they are nursed by their mother or by the foster sow (p > 0.05), it is the same for the controls (p > 0.05). But the control piglets grow more rapidly than the
premature, this trend is clear for the piglets put under the treated sows (p < 0.01), it is less marked for the piglets placed under the controls (p > 0.05). This experiment therefore indicates that the growth of piglets between birth and weaning depends essentially on the piglets and in particular on their prematurity. Lactation therefore seems unaffected by the treatment used to induce premature birth, this is confirmed by several observations made after administration of PGF2a and analogues (27).

McDowell et al. (18) have moreover observed in vitro that PGF2a and PGE2a have no antiauxotrophic effects on milk ejection. The observed frequency of agalactie after PGF2a or its analogues is not greater than that of the controls (27). Some studies have noted that after such treatment the number of animals with the MMA syndrome (Mastitis-Metritis-Agalactia syndrome) is reduced (2, 22, 24, 40, 44).

Finally the prostaglandin treated sows have a normal fertility at the post-weaning oestrus (1, 6, 9, 16, 38, 77).

PGF2a and its analogues are thus useful for inducing farrowing. They should not, however, be used too prematurely in order to avoid increasing post-natal losses and retarding the growth rates of the piglets. Plans for their systematic use have been proposed in order to synchronize all the births and also to suppress farrowings during the weekend. The advantages of using PGF2a or its analogues have often been emphasized: reduction of working time, easier and certainly more efficacious supervision, facilitation of inter-fostering, better use of building facilities and more homogenous groups of sows and pigs at the time of weaning.

REFERENCES


