Theriogenology 79 (2013) 399–408

Contents lists available at SciVerse ScienceDirect

Theriogenology

journal homepage: www.theriojournal.com

Review

The use of prostaglandins in controlling estrous cycle of the ewe: A review

Sergio Fierro [a,*], Jorge Gil [b], Carolina Viñoles [c], Julio Olivera-Muzante [a]

[a] Departamento de Salud en los Sistemas Pecuarios - Área de Producción y Sanidad Ovina - Instituto de Producción Animal- Facultad de Veterinaria, Paysandú, Uruguay
[b] Departamento de Salud en los Sistemas Pecuarios - Teriogenología - Instituto de Producción Animal- Facultad de Veterinaria, Paysandú, Uruguay
[c] Instituto Nacional de Investigación Agropecuaria, Programa Nacional de Carne y Lana, Tacuarembó, Uruguay

ARTICLE INFO

Article history:
Received 9 December 2011
Received in revised form 17 August 2012
Accepted 28 October 2012

Keywords:
Ovine estrus synchronization
Prostaglandin
Ovulation rate
Fertility
Timed artificial insemination
Sheep

ABSTRACT

This review considers the use of prostaglandin $F_{2\alpha}$ and its synthetic analogues (PG) for controlling the estrous cycle of the ewe. Aspects such as phase of the estrus cycle, PG analogues, PG doses, ovarian follicle development pattern, CL formation, progesterone synthesis, ovulation rate, sperm transport, embryo quality, and fertility rates after PG administration are reviewed. Furthermore, protocols for estrus synchronization and their success in timed AI programs are discussed. Based on available information, the ovine CL is refractory to PG treatment for up to 2 days after ovulation. All PG analogues are effective when an appropriate dose is given; in that regard, there is a positive association between the dose administered and the proportion of ewes detected in estrus. Follicular response after PG is dependent on the phase of the estrous cycle at treatment. Altered sperm transport and low pregnancy rates are generally reported. However, reports on alteration of the steroidogenic capacity of preovulatory follicles, ovulation rate, embryo quality, recovery rates, and prolificacy, are controversial. Although various PG-based protocols can be used for estrus synchronization, a second PG injection improves estrus response when the stage of the estrous cycle at the first injection is unknown. The estrus cycle after PG administration has a normal length. Prostaglandin-based protocols for timed AI achieved poor reproductive outcomes, but increasing the interval between PG injections might increase pregnancy rates. Attempts to improve reproductive outcomes have been directed to provide a synchronized LH surge: use of different routes of AI (cervical or intrauterine), different PG doses, and increased intervals between PG injections. Finally we present our point of view regarding future perspectives on the use of PG in programs of controlled sheep reproduction.

1. Introduction

Prostaglandin $F_{2\alpha}$ and its synthetic analogues (PG) have been studied extensively since its discovery in 1970 as a powerful luteolytic agent [1]. Although progestagen-based protocols are preferred by technicians and farmers to manage reproduction of the flock [2], they have the potential for environmental contamination because of residual progesterone (P4) in used devices and the addition of antibiotic agents to avoid vaginitis [3,4]. Because consumers demand foods produced by "clean, green, and ethical" methods [5], PG are a good alternative, because they are rapidly metabolized in the lung and therefore not accumulated in tissues [6,7].

The use of unsynchronized estrous behavior requires considerable labor in large flocks, complicating the use of other assisted reproductive techniques under extensive

* Corresponding author. Tel.: +598 472 41282; fax: +598 472 27950.
E-mail address: sfierro33@gmail.com (S. Fierro).

0093-691X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.theriogenology.2012.10.022

production systems. Therefore, PG as an alternative to progestagen-based protocols is certainly a possibility for reproductive management of flocks [8].

This review considers the use of PG in the control of the ewe estrous cycle. Historical and present information regarding the phase of the estrus cycle, PG analogues, doses, follicle development pattern, CL formation, P4 synthesis, ovulation rate (OR), sperm transport, embryo quality, and fertility rates after PG administration are reviewed. Furthermore, protocols for estrus synchronization and their success in timed AI (TAI) programs are discussed. Finally, we present our point of view regarding future perspectives of PG in controlled sheep reproduction programs.

2. Responsiveness of the ovine CL to a PG injection

It is well known that administration of PG (ICI 80996 im) between Days 5 and 14 of the estrus cycle (Day 0 = estrus) induces luteolysis (rapid luteal regression), followed by estrus and ovulation [9,10]. Acritopoulou and Haresign [10] reported that 50% of the ewes treated on Day 3 showed estrus (2/4), and they suggested that the ewes that responded to the treatment were in a more advanced stage of luteal development compared with those that failed to respond to treatment. Similarly, there were earlier reports [11] that the CL of the ewe is sensitive to prostaglandin $F2_{\alpha}$ (10 mg) given on Days 3 and 4 (2/8) of the cycle. In addition, Rubianes et al. [12] reported that the refractoriness of a recently formed ovine CL to PG might be restricted to the first 2 days after ovulation. These findings were subsequently confirmed by Contreras-Solís et al. [13]. Furthermore, Pope and Cárdenas [14] induced luteolysis in 20% of ewes treated on Day 3.5 using 10 mg of prostaglandin $F2_{\alpha}$. A possible explanation for the relative refractoriness of a young CL (Day 4) might be the greater capability for catabolism of PG, because of enhanced activity of the enzyme 15-hydroxyprostaglandin dehydrogenase compared with a mature CL (Day 13) [15].

To summarize, based on the information available, refractoriness of the ovine CL to a PG dose occurs up to Day 2 postovulation. Therefore, higher doses are required to promote luteolysis during the early luteal phase.

3. Prostaglandin synthetic analogues and dose

Various synthetic analogues were developed with the aim to delay the rapid metabolic degradation of natural $PGF_{2\alpha}$ (reviewed in [16]). For example, the synthetic analogue of prostaglandin 15-[RS]-methyl-13,14-dihydro-$PGF_{2\alpha}$ (ONO 453) described by Hughes et al. [17], is a potent luteolytic agent in cyclic ewes, effective in doses of 2 mg (minimum luteolytic dose) when it was administered after Day 3. The increased potency of this compound on the reproductive tract is associated with an increase in its biological activity on other tissues (smooth muscle of the vascular system, and gastrointestinal tract), undesirable effects that limited its use in medical and veterinary practice [16]. In addition, the use of another synthetic analogue of PG, ICI 79939, was reported in sheep by Hearnshaw et al. [18]. These authors studied the effects of various doses (15.6, 31.2, 62.5, and 125 μg), and all except the lowest dose promoted luteolysis followed by estrus behavior in ewes.

The most widely used synthetic analogue has been 16-aryloxyprostaglandin (ICI 80996; Cloprostenol) [19], which is 100-fold more potent than $PGF_{2\alpha}$, and with more selective biological properties. The luteolytic effect of ICI 80996 administered im was identical to that produced by a local ovarian infusion via the ovarian artery using $PGF_{2\alpha}$ [16]. Its effectiveness was in part because of the most selective action of this compound on the CL [20] and to its longer life span [16]. An injection of 100 μg of Cloprostenol resulted in a high degree of synchrony in the return to estrus and the timing of the LH peak [9]. Other researchers suggested that the appropriate dose of this analogue was 125 μg [21]. However, doses as low as 50 μg were reported to be effective to induce luteolysis in the ewe [16]. Two active isomers (D and L) and a racemic mixture, DL, of Cloprostenol are commercially available, but only the D-isomer binds to the PG receptors of the bovine CL and myometrial cells, allowing for its luteolytic activity. In addition, because D-Cloprostenol is 10-fold more potent than DL-Cloprostenol [22], a lower dose of the isomer D is effective.

Another analogue used in sheep reproduction is ONO 1052 (Delprostenate). Bonifacino and Aragunde [23] reported that the lowest effective dose in a single injection regimen was 40 μg; however, when a double injection regimen was applied, the effective dose may be decreased to 35 μg. Despite the promising results using this prostaglandin analogue, few articles have reported its use in sheep reproduction [12,24–28].

Loubser and van Niekerk [29] used two doses of Dinoprost 11 days apart, achieving promising results with 10 mg per dose compared with 5 mg. Other researchers used this analogue to study the effects of PG on uterine motility and sperm transport [30–35]. The interval between two doses on reproductive results was studied in other reports [36] with acceptable reproductive results.

To conclude, considering the effective doses for each analogue, all products described above could be used for estrus synchronization in sheep. However, there is a positive association between the dose administered and the percentage of ewes that respond to the treatment by showing estrous behavior [14,29,37].

4. Progesterone decrease, follicle development, steroidogenic function, OR, and CL life span, after PG administration

The decrease in plasma P4 concentrations is more pronounced after luteolysis induced by PG compared with natural luteolysis [38,39]. Complete luteal regression is achieved from 6 to 24 hours versus 72 hours (induced vs. natural luteolysis, respectively [40–42]).

Early reports indicated that characteristics of the LH discharge after PG administration were similar to control untreated ewes [9,40,43]. However, a second smaller discharge of LH occurred 7 to 8 hours [41] or 10.5 hours [44] after PG injection. Probably, the initial peak of LH released during PG administration stimulated the ovary to secrete