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Historical perspectives and recent research on superovulation in cattle

Gabriel A. Bó [a,b,*], Reuben J. Mapletoft [c]

[a] *Instituto de Reproducción Animal Córdoba (IRAC), Córdoba, Argentina*
[b] *Instituto A.P. de Ciencias Básicas y Aplicadas, Medicina Veterinaria, Universidad Nacional de Villa María, Córdoba, Argentina*
[c] *Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

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ABSTRACT

Superovulation protocols have evolved greatly over the past 40 to 50 years. The development of commercial pituitary extracts and prostaglandins in the 1970s, and partially purified pituitary extracts and progesterone-releasing devices in the 1980s and 1990s have provided for the development of many of the protocols that we use today. Furthermore, the knowledge of follicular wave dynamics through the use of real-time ultrasonography and the development of the means by which follicular wave emergence can be controlled have provided new practical approaches. Although some embryo transfer practitioners still initiate superstimulatory treatments during mid-cycle in donor cows, the elective control of follicular wave emergence and ovulation has had a great effect on the application of on-farm embryo transfer, especially when large groups of donors need to be superstimulated at the same time. The most common treatment for the synchronization of follicular wave emergence for many years has been estradiol and progestins. In countries where estradiol cannot be used, practitioners have turned to alternative treatments for the synchronization of follicle wave emergence, such as mechanical follicle ablation or the administration of GnRH to induce ovulation. An approach that has shown promise is to initiate FSH treatments at the time of the emergence of the new follicular wave after GnRH-induced ovulation of an induced persistent follicle. Alternatively, it has been suggested recently that it might be possible to ignore follicular wave status, and by extending the treatment protocol, induce small antral follicles to grow and superovulate. Recently, the mixing of FSH with sustained release polymers or the development of long-acting recombinant FSH products have permitted superstimulation with a single or alternatively, two gonadotropin treatments 48 hours apart, reducing the need for animal handling during superstimulation. Although the number of transferable embryos per donor cow superstimulated has not increased, the protocols that are used today have increased the numbers of transferable embryos recovered per unit time and have facilitated the application of on-farm embryo transfer programs. They are practical, easy to administer by farm personnel, and more importantly, they eliminate the need for detecting estrus.

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1. Introduction

The objective of treatments to induce superovulation in embryo transfer programs is to obtain the maximum number of transferable embryos with a high probability of producing pregnancies. However, wide ranges in superovulatory response and embryo yield in several different species have been reported [1]. In fact, Gordon [2] stated in 1975 that "although superovulation as a method of obtaining a supply of eggs has taken many forms over the years; it still leaves much to be desired. In fact, it must still be regarded as a major problem blocking progress in

* Corresponding author. Tel.: +54 (0) 3543 477214; fax: +54 (0) 3543 477214.
E-mail address: gabrielbo@iracbiogen.com.ar (G.A. Bó).

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exploiting egg transfer in increasing numbers of progeny from genetically superior cattle". Although considerable recent progress has been made in the study of ovarian physiology, manipulation of ovarian function and gonadotropin biochemistry, factors inherent to the donor animal which affect superovulatory response are only partially understood. Thus, a high degree of unpredictability in superovulatory response still exists more than 35 years later, creating problems which affect the efficiency and profitability of commercial embryo transfer.

The earliest reports on superovulation in cattle and sheep came from Wisconsin, in the United States (cited in [2]). Basically, gonadotropins were administered several days in advance of the anticipated normal estrus in an effort to induce multiple ovulations. This was often followed by an injection of human chorionic gonadotropin (hCG) approximately 5 days later (or at the onset of estrus) to induce ovulation. Although studies on the use of anterior pituitary preparations from sheep, horse, cattle, and pigs were reported (cited in [2]), the use of equine chorionic gonadotropin (eCG or PMSG) became the standard approach. Betteridge [3] indicated that in the early days of bovine embryo transfer there was general consensus that eCG had to be administered during the transition from the luteal to the follicular phase, at approximately Day 16 of the estrous cycle, in animals undergoing natural luteolysis. In that regard, Hafez et al. [4] developed a protocol that was widely used in the cow; 2000 to 3000 IU of eCG was administered on Day 16 of the cycle, followed by 10 mg of estradiol-17β on Day 19 and 20 and 2000 IU of hCG on Day 21. It was intended that the estradiol would ensure luteal regression, but a more important consequence was that most donors showed estrus [2]. This protocol became the standard superovulation protocol used at that time.

The introduction of commercial preparations of $PGF_{2\alpha}$ in the 1970s resulted in its use in superovulation protocols. Elsden et al. [5] reported that donors that received $PGF_{2\alpha}$ 48 hours after the administration of eCG appeared to have higher superovulation rates than those that simply received eCG on Day 16 of the cycle. The use of $PGF_{2\alpha}$ also meant that it was possible to initiate gonadotropin treatments at other times during the estrous cycle and most practitioners began treating with gonadotropins during midcycle. Indeed, Phillippo and Rowson [6] reported a higher superovulatory response when eCG was administered between Days 8 and 12 than when it was administered at other times during the estrous cycle. This has subsequently been demonstrated to be at the approximate time of emergence of the second follicular wave [7].

2. Superovulation and commercial embryo transfer

The commercial embryo transfer industry in North America developed in the early 1970s with the introduction of continental breeds of cattle which were then in short supply. Superovulation and embryo transfer offered the means by which their numbers could be increased rapidly. Although eCG was used initially (reviewed in [2,3]), intense research resulted in very rapid changes in practitioner's approaches to superovulation. In 1978, Elsden et al. [8] reported a greater superovulatory response after treatment with a crude pituitary extract containing FSH plus 20% LH compared with the use of eCG. Monniaux et al. [9] also observed that ovulation rate and the percentage of cows with more than three transferable embryos tended to be greater after the use of a pituitary extract containing FSH rather than eCG. However, others found no differences between pituitary extracts containing FSH and eCG [10,11]. Endocrine studies have revealed that eCG-treated animals more frequently had abnormal profiles of LH and progesterone [12,13] which was associated with reductions in ovulation and fertilization rates [14] compared with FSH-treated cows.

The main reason that most practitioners switched from eCG to FSH was related to problems associated with the prolonged stimulation of the ovaries after a single injection of eCG. The half-life of eCG has been shown to be 40 hours in the cow and eCG persists for up to 10 days in the bovine circulation [15]. The long half-life of eCG causes continued ovarian stimulation, unovulated follicles, abnormal endocrine profiles, and reduced embryo quality [13,16–18]. The problems associated with the half-life of eCG were largely overcome by the intravenous injection of antibodies to eCG at the time of the first insemination, 12 to 18 hours after the onset of estrus [19,20]. Unfortunately, the pharmaceutical company that developed a commercial monoclonal antibody to eCG (Neutra-PMSG; Intervet, The Netherlands) discontinued the product in the 1990s. Another hormone preparation used in human fertility clinics, human menopausal gonadotropin (hmG), has also resulted in a superovulatory response that was comparable with pituitary extracts [21]; however, it has not been used extensively by practitioners because of its high cost.

Most cows nowadays are superstimulated using pituitary extracts containing FSH. However, there is also a large amout of LH in crude pituitary extracts, and there is considerable variability in FSH and LH content of all crude gonadotropin preparations [22]. Radioreceptor assays and *in vitro* bioassays have revealed variability in the FSH and LH activity of eCG, not only among pregnant mares, but also within the same mare at different times during gestation [15]. The effects of the FSH/LH ratio of eCG on the superovulatory response has been examined and there was a positive correlation between the ratio of FSH/LH activity and superovulatory response. Lower ratios of FSH/LH activity resulted in a reduced ovulatory response in immature rats and LH added to eCG reduced the superovulatory response in cattle [15,22].

Purified pituitary extracts with low LH contamination have been reported to improve the superovulatory response in cattle. Chupin et al. [23] superstimulated three groups of dairy cows with an equivalent amount of 450 μg pure FSH and varying amounts of LH and showed that the mean ovulation rate and the number of recovered and transferable embryos increased as the dose of LH decreased. It has been suggested that high levels of LH during superstimulation cause premature activation of the oocyte [16]. Although several experiments with an LH-reduced pituitary extract [24] using several different total doses ranging from 100 to 900 mg of NIH-FSH-P1 revealed no evidence of detrimental effects of dose on embryo quality [25,26], doubling the dose of crude pituitary

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