

Uses and Abuses of Hormones and Their Analogs in Estrus Synchronization, Control of Parturition, Prophylaxis and Therapy of Infertility

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Hormones are an increasingly important part of the veterinarian's armory in battling infertility, maintaining fertility and controlling cycle and parturition. Therapeutic, prophylactic and biotechnical aspects of their use can often no longer be separated: Cycle control methods have become tools to treat or prevent certain aspects of infertility; methods to control parturition as a management tool are of importance to terminate pathological gestations or alleviate dystocia and enable obstetrical procedures.

Drug laws worldwide assure use or dispensation of these hormones by veterinarians only.

The rowing of issues in the title of this presentation, to be discussed in this introductory review, does not reflect a ranking of their present importance. But it may well reflect its future importance. The order of discussion chosen here follows the biological and biotechnical sequence of events in the life of an animal of the bovine species and the chances to be subjected to hormonal treatments.

In trying to cover such extended grounds, this reviewer has to rely heavily on previously published accounts on some of the many issues involved (1, 2, 3, 4, 51-h) and a recently published book in which an attempt was made to cover most of this review's subjects in some depth (6). Further on, one has to account for regional and national differences in drug availability. The availability of progestins and several prostaglandins in Western Europe is contrasted by the lack of progestins and the availability of only one prostaglandin in the U.S. Hence, aspects have to be covered that are relevant to only part of this audience. In addition, reference will be made to a system in which the theriogenologist of the future will build his own approaches to the hormonal control of normal and abnormal reproductive functions by using what is available to him locally, and in sequences and dosages which are not always in compliance with recommended or governmentally approved uses - as long as consumer safety (aspects of milk and meat residues) remain assured.

A. Legitimate Uses of Hormones

1. *Estrus Cycle Synchronization.* After decades of false alarms or cumbersome solutions (daily progesterone injections or daily feedings of such progestins as MAP, CAP and MAG for 12 to 18 days: 1, 5b, 6) easy applicable and removable progestins are here (the

Syncro-Mate-B norgestomet implant system; the progesterone coated plastic coil for intravaginal use, PRID: 3, 5d, g, 6). The availability of luteolysins in combination with them (estradiol esters at their insertion or prostaglandins around their removal) have allowed to reduce the time progesterone effects are needed to 6 to 9 days, by this shortened schedule avoiding the previously well known and much discussed fertility depressing effect of these agents (1, 5b and g, 6, 7)

Prostaglandins (PGs) themselves have become a powerful tool for cycle control (5b and g, 6). The one-or-two-injections cycle control method finally seems to have arrived and a dream of many seems to come through and become true.

Veterinarians by now have become well aware of the problems all these new techniques create - in spite of the well documented fact that their correct use, in the correct setting, provides such a degree of synchronization that virtually all systems available allow blind A.I. at predetermined hours (3, 5b, and g).

Prostaglandin F_{2a} as well as all its analogs require not only cyclic corpora lutea to act on, but also the capability of treated animals to resume cycling immediately after such an interference, if necessary twice over 10 to 12 days. Only well managed herds and well selected animals will respond predictably to the investment into these drugs, without creating disappointment, frustration and often undeserved accusations against the drug's effectiveness (5a, g, 6, 8, 9, 10, 11, 12). This is a shortcoming since every herd consists of unknown subpopulations of firmly, regularly cycling individuals of those animals cycling on and off or entirely irregular, and of those not cycling at all. In the past, the use of progestins frequently allowed to ignore such unknowns. Progestins control regular and irregular cycles alike, and often act as a "cycle starter" (2, 5b, d, g, e, 6). This effect has been instrumental in part for the success reported when both treatment schedules are combined (3, 5b, g, 12). The future may well belong to such a scheme, where either the 6 or 7 day use of Syncro-Mate-B (without estradiol) or of PRID is supplemented by a PG injection at the day of withdrawal or 24 h. earlier.

These new schemes for cycle control are finding increasing use in beef and dairy heifers, also in nursing beef and lactating dairy cows as soon as regular cycles are established postpartum. Preparing a herd for the successful use of such systems is probably one of the most important tasks of veterinary supervised herd health services of the future. Only herds in which the most sensitive index for management - the first service conception rate - is up to industry standards (50% or more) will achieve the desired results from synchronization (13).

2. Control of Parturition:

Only in the last decade and initially not as a result of any concerted effort to find tools for controlling parturition, were methods developed which allow manipulations of parturitions. With them, one can either shorten the gestation period for an early parturition, or assure parturition at a desirable time of the day or the week, or at a desirable gestation length (avoiding delayed gestation) (4a, b, 5c, h, 6). These methods allow us to terminate pathological gestations (4a, b, 5c, 14). and prolonged gestations (15a, b). With the principle of control of parturition established as a desirable goal, efforts to postpone or delay parturition, for short time periods, became attractive (5c, 6, 16).

In principle, all methods to shorten gestations use the same mechanism: luteolysis, by either endogenous prostaglandins, produced under the influence of exogenous hormones like certain glucocorticoids and/or estrogens (4a, b, 5c, 6). Prolongation of gestation - for a limited number of hours - can be best achieved by temporarily paralyzing myometrial activity by a specific B₂-receptor agonist (4b, 5c, h, 16). Neither method - with the exception of really prematurely delivered calves - adversely affects the calf's viability. Induction of parturition, if it occurs before term, results in a high level of placental retainment - a complication of little concern to beef breeders, but of much concern to the dairy producer. This healthy retained placenta - resulting from a desynchronization of the normally well synchronized departure of fetus and placenta - needs time to mature, i.e. to go to its own term. Systemic - not local - antibiotics helps to achieve this goal. Of the treatments to prepare the placenta for a simultaneous early delivery of fetus and placenta, weeklong application of low doses of certain long acting glucocorticoids is the most successful (17). This treatment, followed by a boost with a short acting dexamethasone ester assures parturition at the wanted time, a viable calf and shedding of the placenta (17).

Postponement of parturition by a highly specific B₂2 memetic agent (Planipart B₂ mimetic R) features dominantly in this session. From this reviewer's viewpoint, one of the most important observations so far is the frequently made observation that parturitions, either postponed or interrupted seem to go easier and faster. This aspect deserves

great attention and further detailed exploration, especially in first-calf-heifers where dystocia is a well recognized problem. The advantages such treatment has in obstetrical conditions are self-explanatory. The question how attractive the aspect of prevention of parturition during certain hours (e.g. nights) will be to the cattle industry is still open. The use of induced parturition as a tool to synchronize parturition with milk fever prophylaxis will be reported in this session.

3. Fertility Phophylaxis:

As early as 1966, the early use of cycle control methods in the postpartum dairy cow for the assurance of a short calving interval and the successful prevention of infertility due to anestrus or acycia was reported (18). Since then - first slowly, but by now with an increasing recognition of the problems' economic importance, as the papers in this section are showing - this approach of hormone use is becoming more firmly established. Methods used in this respect in the dairy industry can be summarized as followed:

Initiation of cyclic functions by GnRH or one of its analogs, at about day 15 postpartum; often followed by a prostaglandin in a suitable interval (5e, 6); or initiation of cyclic functions by a progestin withdrawal or 10 to 12 days thereafter; or as soon as the presence of cyclic functions is established by milk progesterone or rectal exploration, any of the above mentioned "classical" cycle synchronization treatments are used (5e, 6). The goal is uniformly a shortening of the calving interval to the optimum of 11.5 to 12 months (5e, 6), the discovery of problem cows early on and their cure and/or elimination as soon as economics dictate. This can involve individual treatments or the treatments of small groups in fixed interval to parturition.

In beef cows, this involves the use of cycle synchronization techniques as soon as cyclic functions are restored (or are expected to be restored in the majority of the population), often coinciding with the beginning of the breeding season. (5e, 6).

4. Infertility Therapy:

Specific neurohormonal or pharmacological aspects of hormones (and their analogs) have become indispensable therapeutic tools for the veterinarian:

Resting or insufficiently working ovaries are stimulated directly by releaser hormones or gonadotropins, or indirectly via positive feedbacks by the shorter term use of sex steroids (natural estrogens; estrogen-androgen-combinations), or negative feedback (the use of progestins as an "artificial corpus luteum") (6).

Silently cycling animals are challenged by similar methods or are "exposed" by luteolytic prostaglandins; ovarian cysts are treated, preferably after a milk progesterone determination, with either luteotrophic hormones (hCG, GnRH and analogs) or luteolysine (PGs). If this diagnostic tool is not available, the use of a luteolysine, followed shortly by a luteotropin has been

recommended (19), or the application of progestins as an "artificial corpus luteum" (6). The pharmacological action of hormonal substances comes into play when PGs are used for the emptying of a pyometra (6) or the treatment of endometritis, as it will be reported at this session later.

This condensed, and by no means complete overview of established hormone uses can nevertheless serve as a baseline and background for comments on hormonal abuses as they may occur inadvertently, by misinterpretation of hormonal actions or by uses to which hormones are not suited.

B. Abuses of Hormones

The probably most widespread hormonal abuse in the control or therapy of cyclic functions occurs when hormones are applied for either biotechnical or therapeutic purposes, in individual animals or herds not suitable and/or prepared to respond to such treatments adequately.

These are either sick animals, which due to their overall impaired condition have ceased to cycle properly, or are acyclic. These animals can not respond to treatment by hormones or may respond only partially, thus creating a new problem in course. Similarly, due to insufficient management, health care and nutrition, entire herds can be called "sick" and are not capable to respond appropriately. Large scale use of hormones in such herds may create an embarrassment for veterinarian and owner alike. Such hormonal abuses and the lack of reaction - or abnormal reactions may have diagnostic value, but of a kind not cherished by anyone.

As a safeguard, a checklist-approach is recommended, which allows an indepth penetration of the herd's condition, and helps to identify and correct problems and to hold off hormone-eager owners, who want to overcome their problems by investing into an expensive single-shot-approach. This approach helps to convince such owners that an investment in health care, nutrition and management has to come first, before hormones can be used with satisfactory results.

There is a great gray area in which the professional judgment of the veterinarian becomes decisive: when is an animal, a herd, recovering from deficiencies of any kind, ready to respond to hormonal treatment? Recovering animals often will not resume reproductive functions quickly. Here, if applied correctly and wisely, hormonal treatment can buy time and can assure a return to economically more favorable conditions over a shorter time. Here hormones can buy time.

Another abuse of hormones can occur when a technique or therapy is used contrary to the animals' seasonal responses. Zebu and Zebu (Brahman) crosses are "seasonal" breeders with a fertility peak in late spring and summer and a nadir in autumn and winter (20a, b). Synchronization "against" the season will cause

unsatisfactory results (21).

Hormones can be abused in heifers too young or too light to respond, or in postpartum cows too close to parturition or too heavily stressed by nursing. Hormones can be abused for indications in which no proof for their usefulness exists, e.g. in the widely promoted use of estrogens early postpartum, especially the widely promoted use of estrogens early postpartum, especially in case of postpartal metritis or endometritis (6). On the other hand, the value of progestins helping to control such postpartal disturbances is often overlooked (6).

From what has been said above, it is clear that the use of PGs without assurance that animals either cycle or have cysts can be called an abuse.

In the treatment of ovarian cysts, frequent use of HCG can create a state of refraction. This had been thought to result from antibody formation. This section will provide further comments on the pro and cons on that subject. One of the advantages of GnRH and its analogs is their lack of antigenicity. One of the potential abuses of GnRH is its employment to treat those temporarily stationary follicles in dairy cows early postpartum, which disappear in most instances spontaneously.

Another protein hormone, PMSG, has been accused of causing antibody formation and consequently a loss of responsiveness (22a, b). Experiences with PMSG for repeated superovulations seems to refute this claim (23). Further research is needed in this area.

In the *control of parturition*, hormonal misuse is equally possible. High doses of long acting corticoids (triamcinolon, certain dexamethasone esters; flumethasone suspension) (4b, 5c) can cause early parturition of fetus *and* placenta, but elevates the stillbirth rate to unacceptable levels. Using progesterone close to term to prevent early parturition is successful but results in severe dystocia and high stillbirth rate thereafter (24). Beta-2-stimulators, for the interruption of parturition, become ineffective if the myometrium, as in stage 2 of labor, is already under oxytocin dominance (25).

A special case of hormonal abuse is given if animals are endangered by hormonal overdosing, or edible products from animals are tainted with hormonal residues by such overdosing, or by not obeying to the mandatory withdrawal times now posted at any package insert. The pharmaceutical industry not only has been forced to include these withdrawal time statements, but overdosing or unjustified therapeutic applications were widespread, e.g. for certain estrogens like DES or long acting estradiol esters like ECP.

There is no contradiction in the promotion for self-composed systems of reproductive function control or therapy, and the responsibility for the prevention of hormonal abuses of any of the kind enlisted above. The

veterinarian challenged with the hormonal control of normal and of abnormal reproductive functions, is at the same time the safekeeper of these hormones, appointed to this position by the law of most lands. His training and his continued education, combined with his sense of responsibility for animal welfare, the owner's economic survival and the public health aspect involved, should allow him to make the right decisions.

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