IS THERE A FUTURE FOR PHARMACEUTICAL MANAGEMENT IN COW REPRODUCTION? EUROPEAN PERSPECTIVE

Sylvie Chastant-Maillard

Unité de Reproduction, Ecole Nationale Vétérinaire, Alfort, Maisons-Alfort, France
schastant@vet-alfort.fr

1. INTRODUCTION

Pharmaceutical management of reproduction consists in the systematic administration of one molecule or an association of several to all the cows of a herd. The aims are an improvement of work organization and prevention of cattle illnesses. Systematic programs can be used:

- to control insemination time: estrus synchronization and/or induction/ovulation induction,
- to control calving period: calving induction,
- to decrease the incidence of puerperal and post partum complications (prevention of placental retention, of acute puerperal metritis, of chronic post-partum metritis).

Additional treatments such as hCG, GnRH, eCG, progesterone, … have been explored to decrease embryonic mortality. They will not be addressed here (Binelli et al. 2001; Macmillan et al. 2003; Thatcher et al. 2006).

In this presentation, will be reviewed the potential objectives for the farmer, the protocols available, their efficiency and their social acceptability in Europe.

2. WHICH AIMS FOR THE FARMER?

The mean herd size in Europe is increasing (Institut de l’Elevage, 2003), due to milk production quota and new environmental norms, imposing new investments in livestock building. Amount of work necessary to conduct herds is thus increasing. Conversely, farmers wish to have access to leisure, as other professional branches. To date, in dairy herds, the tendency is to simplify milking, for example by the suppression of Sunday evening milking or the use of a milking automate. Moreover, low profitability of cattle production, difficulties of every day life, tend to make people drift away from this type of work: the number of employees present on cattle farms in Europe remains very low.
From these trends (Sheldon et al. 2006), arises the necessity to simplify time-consuming tasks in herd management. Concerning reproduction, three tasks are especially time-consuming:

- precise estrus detection for insemination; Using artificial insemination, estrus detection is crucial and requires a large amount of work. Estrus detection is made more and more difficult by the increase of herd size, of average milk yield, and the housing in free stall systems. Consequences are short duration of estrus (14 h in mean for cows, 10 h for heifers), abnormal postpartum cycles (short or long), poor expression of estrus behaviour (increase of the incidence of silent heats). An accurate detection requires at least 2 observation periods at 7:00 and 22:00, from 15 minutes each, without any perturbation for the animals (that implies that farmer cannot feed, treat or milk them at the same time he observes animals for estrus detection). Estrus detection rates in dairy herds are often less than 50%.

- observation of cows at the end of pregnancy for calving supervision (in order to prevent calf mortality due to dystocia); the difficulty is due to the huge variability in pregnancy duration: calving are dispersed on 20-24 days around the mean time (Bosc, 1981). Moreover, no simple management solutions such as modification of meal time (Pennington & Albright, 1985) can restrict calving occurrence in the daylight period and avoid the farmer to wake up at the night to survey potentially calving cows.

- observation of all cows for pathology detection. Post partum cows are particularly to be observed. When necessary, treatments are also time-consuming, since they last usually several days, require the restraint of the animal, supervision for recovery and complications. The objective of a systematic pharmaceutical administration would be to decrease morbidity, both for animal welfare, to restore their production capacity and to decrease time spent in individual treatments.

The farmer can be helped in these tasks by mechanical or electronic detection systems (for estrus and calving detection) and also by pharmaceutical treatments aiming to control the release of these events. Moreover, pharmaceutical management of reproduction requiring the constitution of small clusters of females, homogenous lots of calves will be born (thought to synchronized calvings), more easy to breed (heifers), to sell (males) with a decreased morbidity/mortality rate (provided lots separation).

Since beef herds resort neither to artificial insemination (in Europe, less than 10% of beef cows are inseminated) nor calving induction (because of increased calf mortality), dairy herds are mainly concerned by pharmaceutical management.

3. PROTOCOLS AVAILABLE IN EUROPE - MEDICAL EFFICIENCY

The main differences between pharmaceutical possibilities in Europe and in the United States concerning reproduction management are the interdiction of estrogens and bovine somatotropin in Europe and to date (May 2006) the non availability of GnRH agonist implants. In 1986, the use has been restricted only to estrus synchronization. But since the 14th October 2006, these molecules are completely forbidden. Neither for pathological conditions (such as metritis), nor for estrus synchronization are estrogens now banned.

3.1 Synchronization of estrus and/or ovulation

Protocols are based on prostaglandins, progestagens, or an association GnRH-prostaglandins (Nebel & Jobst, 1997; Thatcher et al. 2001; Grimard et al. 2003; Lucy et al. 2004; Yamada, 2005). Interest for protocols controlling follicular waves and ovulation time is hugely growing since 10 years.
A wide range of reproductive systems are practiced on dairy farms. These systems can range from no hormonal intervention (cows inseminated after detected estrus), low hormonal intervention (restricted to problem cows) to high hormonal intervention where reproductive cycles are controlled for programmed inseminations.

### 3.1.1 Synchronization of estrus

**Prostaglandins F2α**

This classical protocol (two injections of prostaglandins F2α (natural or analogue) 11 to 14 days apart) is efficient only on cycled females. Pregnancy rate is 22-58%. Since prostaglandins F2α do not control follicular waves, females come in estrus between two and six days after the second injection. It is thus still necessary to perform estrus detection for insemination, even if the observation period is restricted to less than one week. It is also possible to systematically inseminate at 72 and 96 hours after the second injection, but pregnancy rates are significantly lower.

**Progestagens**

The progestagen based protocols have been slightly modified since estrogens banning. They now systematically associate prostaglandins F2α and progestagens, with or without GnRH analogue buserelin (Figure 1). Pregnancy rate is 40-70%. These protocols are the only ones to not only synchronize, but also induce estrus cycles.

![Diagram of modified progestagen-based protocols for estrus synchronization](image)

**Figure 1: Modified progestagen-based protocols for estrus synchronization**

### 3.1.2 Synchronization of ovulation

These protocols are the most recently tested, based on the founding work was from Pursley *et al.* (1995). This new generation aims to get rid of estrus detection, in synchronizing ovulations. To date, these solutions are rarely chosen for systematic breeding in Europe.

**World Buiatrics Congress 2006 - Nice, France**
**Association GnRH-prostaglandins-GnRH (GPG)**

An injection of GnRH or an analogue is followed 7 days later by the injection of prostaglandins F2α (natural or synthetic). Another injection of GnRH or analogue one day after allow ovulation synchronization: artificial insemination is performed 12-16 hours later, on Day 10 after the first injection. The main interest of this protocol is to allow fixed time insemination, without estrus detection. Pregnancy rate is 22-53%. This protocol gives satisfying results only for cycled cows, but the primary drawback of GPG systems is the low conception rate. It should not be used for heifers, and not in non cycled females, because of even worse pregnancy rates.

**Presynchronization**

GPG is more efficient if treatment begins when cows are at Day 5 to 12 of the estrus cycle. Significant increase (+ 10 points) in pregnancy rates is obtained with a presynchronization with two prostaglandins injections 14 days apart, 12 days or more before initiation of GPG.

**GPG + progestagens**

The main interest of GPG is to allow insemination without estrus detection. Nevertheless, 20% of the treated animals come in estrus on another day than Day 10 and have to be inseminated when in heat (Mialot et al. 1999). The addition of a progestagen administration between first GnRH injection and prostaglandin eliminates the occurrence of estrus and ovulation before fixed time for AI.

**Second insemination**

Cows not pregnant after the initial AI attempt at estrus synchronization have to be re-inseminated as soon as possible. Ultrasonography can be used to diagnose pregnancy at 29-31 days after insemination, and then, as soon as the diagnosis is established, it is proposed to inject in non pregnant cows PGF2α, followed 48 hours later by GnRH administration to cause ovulation and allow timed AI (Stevenson et al. 2003) (“rapid resynchronization”).

### 3.1.3 Choice of the protocol

Face to a herd containing a majority of anestrus non cycled cows (such as winter-calving beef cows), the only one protocol usable for a global systematic estrus synchronization, is the one based on progestagens. Face to a herd with a large majority of cycled cows (dairy herd or autumn-calving beef cows), all three protocols are indicated; the protocol of lower cost is the first one (two prostaglandins) but it requires animal observation. GPG is more expensive but it allows insemination without estrus detection, at a fixed time.

Even though estrus detection remains necessary for some protocols, the farmer will have the benefit of knowing in which small period of time estrus symptoms can be expected and concentrate his inspection to that period. Whole-herd synchronization followed by estrus detection in pasture-based systems demonstrated a net benefit. It is less clear for timed AI (Lucy et al. 2004): GPG and related protocols allow timed AI without estrus detection, but most of the programmes for synchronization after fixed timed AI are associated with reduced conception rates compared with that of non synchronized animals inseminated on detected estrus (Refsdal, 2000). If all these systematic breeding programs reduce or even suppress time and labour expense for estrus detection, they do not significantly improve pregnancy rates. The exact quantitative prevision of the success rate for whole herd programs is difficult: different herds can respond inconsistently to the same program, due to nutrition, sanitary status of the herd, genetics, and compliance with the protocol.

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3.1.4 All in-all out system

Some have suggested to conduct cow reproduction on the same model than the one used for sows (all in - all out) (Le Page, 1997), with the objective to simplify farmer’s work organization.

The all in-all out system can be based on the three types of protocols described above. The simpler is the administration of two prostaglandins injections performed 14 day apart. Both injections are thus performed the same day of the week (Saturday or Monday, to induce heat 2 to 6 days later during the week) (Table I). Animals are observed during the following week, and inseminated when observed in heat. Return in estrus is observed three weeks after. Drying-off is performed 36 weeks after insemination, calving supposed to occur 44 weeks after insemination. Another group (band 2) is treated 3 weeks later than band 1. Cows of Band 1 coming back in heat are transferred to Band 2. If cows come in estrus a third tentative, they are submitted to clinical examination by a veterinarian. The final aim of this organization is to plan only one type of work by week for the farmer: insemination, drying-off, calving.

Table I: All in - all out system with estrus synchronized with 2 prostaglandins 14 days apart

Numbers refer to band number (Le Page, 1997)

<table>
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<tr>
<th>Week number</th>
<th>1</th>
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<td>1</td>
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<td>Estrus n°1</td>
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<td>Estrus n°2</td>
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<th>Week number</th>
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<td>Drying-off</td>
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<td>3</td>
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Type of work    | INS | CAL | DRY | INS | CAL | DRY | INS | CAL | DRY | INS | CAL | DRY |

INS = insemination
CAL = calving
DRY = drying-off

If this planified organization of reproduction is very efficient in porcine species thought to a very constant duration of pregnancy, it is not in the bovine, due to large variations in pregnancy duration. So in fact, the farmer cannot concentrate on only one activity per week. However, this system provides a protocol at least for systematic breeding.

Combining GPG with rapid resynchronization would limit reproductive management to 3 days a week (Table II). Grouping cows into 3-week cohorts would focus all aspects of herd reproduction to 8 days within a 5-week period (Lucy et al. 2004).

Table II: Calendar for controlled breeding using Ovsynch and rapid resynchronization
A second group of first insemination cows is started during week 4. Cows of Group 1 and 2 are given PGF$_2\alpha$, GnRH, and timed AI on the same days (Lucy et al. 2004).

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<td>PGF$_2\alpha$</td>
<td>GnRH</td>
<td>AI</td>
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<tr>
<td>Week 4</td>
<td>GnRH</td>
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<tr>
<td>Week 5</td>
<td>Pregnancy diagnosis/PGF$_2\alpha$ non pregnant</td>
<td>GnRH non pregnant</td>
<td>AI</td>
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3.2 Calving induction

After 275 days of pregnancy, the classical protocol used for calving induction is a short-acting corticosteroid, associated or not with prostaglandins. Calving is obtained 24 to 72 hours after the injection (Barth, 1986; Claydon, 1984). The two main problems associated with such calving induction is the increase of the incidence of placental retention and, for farmer’s work organization, the quite large interval on which induced cow remains to be observed (up to 3 days). If this treatment sharply decreases the dispersion of calvings (3 days vs 20 days for natural calvings), calving at night cannot be avoided with confidence. Nevertheless, Ballarini et al. (in Gilbert & Schwark, 1992) proposed an injection of clenbuterol (400 micrograms IM) at 6h PM without regard for the stage of labour of the female. A second dose (200 micrograms IM) was then administered to all animals that have not calved by 10 PM. This protocol seems to be effective in preventing births between 10 PM and 6 AM, permitting better supervision of parturition and more comfortable life for the farmer.

3.3 Prevention of post-partum uterine infections

The molecules can be administrated either to all parturient cows whatever calving conditions or restricted to cows with predisposing factors for uterine infection (retained placenta, vaginal lacerations, dystocia, …).

3.3.1 Prevention of placental retention

Systematic administration of ecobic drugs (myometrial contracturants: oxytocin, ergot derivatives, prostaglandins or β2-adrenoreceptor) 12 hours maximum after parturition give unpredictable and poor results in term of prevention of retained placenta (Peters & Laven, 1996). The administration of collagenase via umbilical vessels or ovario-uterine arteries has also not proven its efficiency and practicability.

3.3.2 Systematic intra uterine antibiotherapy on the day of calving

3.3.3 Systematic administration of prostaglandins F2α (Day 1 to Day 30)

Results are controversial and the delay between calving and treatment may play a role. A meta-analysis including 24 trials on 4000 animals concludes that systematic administration of prostaglandins does not significantly decrease the number of days open, even when restricted to cows with abnormal puerperium (2.6 days for all cows, 3.3 days for cows with abnormal puerperium; Burton & Lean, 1995).

3.3.4 Parenteral administration of antibiotics

The aim is to diminish the severity of the affection or to reduce incidence of acute puerperal metritis and associated affections (abomasal displacement, ketonemia, pyelonephritis, reticuloperitonitis,
Systematic management can be a strictly preventive attitude (injected cows are the ones suffering of placental retention or from another risk factor such as vaginal laceration or dystocia; preventive treatment) or a precocious curative treatment (association of a risk fact or and an hyperthermia).

Only ceftiofur has been tested in these indications. As a precocious treatment, ceftiofur gives recovery rates equivalent to those obtained by manual membranes removal associated to local antibiotics (Drillich et al. 2003). In cows affected with retained fetal membranes only (preventive treatment), administration of ceftiofur during 5 days since the second day post partum decreases the incidence of puerperal metritis (13% vs 42%) (Risco & Hernandez, 2003). Nevertheless, no difference has been evidenced on uterine involution patterns and on reproductive performance for both studies.

4. GLOBAL INTEREST FOR THE FARMER?

From what has been presented above, it can be seen that the medical or zootechnical efficiency of systematic protocols is questionable. Moreover, most published studies have been conducted in the US: their results are perhaps not be extended automatically to European herd conditions. Their economic interest is also questionable and difficult to predict and evaluate, depending on each production system, incidence of post partum infections, difficulties for estrus detection, pharmaceuticals cost: on one hand, eventual reduction of the number of employees, eventual increase in reproductive performance, decrease of the morbidity rate, thus decrease in veterinary cost and suppression of production loss - on the other hand, increase in pharmaceuticals consumption. Economical evaluation calculated in one country is also probably of little value in other countries (Nebel & Jobst, 1998). For example, costs for hormone are very different in the US and in France: the mean cost for a prostaglandin dose is respectively of 2.6 € and 9 €; the mean cost for a GnRH or analogue dose is respectively 5.8 € and 15 €.

Pharmaceutical management of reproduction may be effective and of economical interest only in herds with below average mean conception rate or bad estrus detection rate (Young, 1989; Mialot et al. 1999; Kristula & Bartholomew, 1998). The modifications in GPG program such as presynchronization or timed AI at the time of second GnRH injection (Cosynch) may be useful alternatives for reproductive management in dairy herds with less than optimal estrus detection rates (Rabiee et al. 2005; El-Zarkouny et al. 2004; Navanukraw et al. 2004). GPG by itself is already interesting in herds with low estrus detection efficiency, since 100% cows will be submitted to AI (Lucy et al. 2004). However, the use of hormones and antibiotics to solve or mask managerial problems should be avoided. It is important for producers to realize that such reproductive management systems cannot solve all reproductive problems per se. For instance, incidence of cows in anestrus greatly reduces the reproductive efficiency and will not be resolved solely by synchronization systems. Moreover, calving induction is associated with placental retention and calf mortality (Macmillan, 2002). Pharmaceutical management can bring some solutions for decreasing work charge but not for improving reproductive performance.

Moreover, pharmaceutical management of reproduction does not automatically mean global decrease in working time, but rather changing in the type of work: observation time (estrus, calving), nursing and treatment of ill animals are (at least partially) replaced by systematic treatments, i.e. time for sort, restraint and molecule administration. Some suggest to perform injections in the milking parlour to simplify the operations, but some others avoid this solution in order not be render cows reluctant to enter milking parlour. Farmer has also to respect injections programs. Since protocols are sometimes complex, with their efficiency depending on the respect of...
time interval between injections (GPG, for example) (Thatcher et al. 2001), the compliance of treatments can be also problematic. A precise and up-dated follow-up of the herd is also necessary. Farmer has also to accept to record all data about molecules injected to each cow (“Health card system”). Working time with animals is then concentrated on few hours per day, and “more comfortable” from an intellectual point of view, but requiring rigorous follow-up. Farmers could be helped in systematic management by new professionals. In France, a new professional status is discussed to date, “rural veterinary auxiliary”, who would administer treatments (or perform small surgeries) to ruminants under the supervision and the prescription of a veterinary surgeon. Norwegian regulations do not allow farmers to administer antibiotics themselves, except when following up a treatment established by the veterinarian after a diagnosis in an individual animal has been made (Refsdal, 2000). This new farm partner could play a part in case of development of pharmaceutical management of reproduction.

5. SOCIAL ACCEPTABILITY OF SYSTEMATIC TREATMENTS

In Europe, one important obstacle for pharmaceutical control of reproduction is its societal acceptability. A general scepticism is growing among European consumers concerning the use of hormones and antibiotics in modern farming. People are worried about potentially negative side effects by using hormones and antibiotics in food animals. There is a growing concern about residues in animal products: the recent interdiction of estrogens witnesses the consumer’s anxiety for xenobiotics residues in food products. The suspicion of consumers is still more acute against antibiotics. Evidence of increasing resistance to antibiotics in bacteria infecting humans has focused on the role the anti-microbial drug use in food-producing animals plays in the emergence of resistant bacteria.

Because of the fear for consumer reactions on ethical concerns related to replacement of management with hormones, the Farmers’ Associations decided in Sweden to cease using estrus synchronization as a tool for AI in 1996 (Refsdal, 2000). In Europe, the number of farmers growing organically cultivated foodstuffs is increasing and according to the regulations for organic farming, the use of hormones and antibiotics is limited. Estrus induction, pharmaceutical control of breeding are not permitted.

Moreover, consumers become more and more sensitive to animal welfare: pharmaceutical management of reproduction implies numerous subcutaneous or intramuscular injections, that may be not well accepted. For example, in protocols such as presynchronization before GPG with progesterone supplementation (El-Zarkouny et al. 2004), cows are manipulated six times, receiving 5 injections, one intravaginal device, three different hormones in order to perform only one insemination. Despite the number of injections and the relative inefficiency, presynchronization method is used in North America where many large herd managers feeling that scheduling reproductive treatments and inseminations is simpler and more effective than multiple daily sessions of estrus detection (Lucy et al. 2004). In Europe, such protocols may be far from well accepted, both by farmers and consumers.

6. CONCLUSION

Many structural differences render Europe to date less favourable to systematic pharmaceutical breeding than United States. First of all, the herd size is much smaller in Europe, the cost of manpower is higher. European agricultural policy has been modified in 2003 (compromis de Luxembourg, 26 Juin 2003). It especially modifies the system of subsidies, specialized milk producing herds being the most affected production system. Milk price will significantly decrease (15 to 25%) and milk intensification will increase. This reform may lead to costs optimisation and work simplification (Institut de l’Elevage, 2003). In Australia, the recent severe reduction in milk
prices has led to a reduction in levels of hormonal intervention. The present trend is to simplify the reproduction tasks and reduce the expenditure (Lucy et al. 2004). What will happen in Europe will depend on the ratio between the cost for labour and the cost for hormones and antibiotics. The consumers’ concern and the way of life for farmers have to be taken into account. Moreover, some propose a very low level of pharmaceutical management of reproduction, with a low reproductive pressure, considering that not all cows of a herd have to be pregnant. The objective is to obtain the number of pregnancies necessary to reach the milk production quota and infertile cows (including anestrus and silent heat) are not to be treated. Finally, the consequences of systematic pharmaceutical management on veterinary activities have to be evaluated: the veterinarian would probably concentrate less on ill cows’ treatment, but more on prevention, on global approach of the herd.

7. SUMMARY

Pharmaceutical management of reproduction corresponds to the systematic administration of hormones or antibiotics, for estrus synchronization, ovulation synchronization, calving induction and prevention of postpartum uterine infections. The aim is to facilitate reproduction management in large herds and to decrease the labour charge of the farmer. Nevertheless, such systems do not systematically improve reproductive performances and their economical interest has to be evaluated in each herd. Their use is also limited in Europe by the consumers’ reluctance to a wide use of xenobiotics in food animals.

8. KEY-WORDS

Estrus synchronization, post partum pathology, hormones, antibiotics, social acceptability.

9. RESUME

La gestion pharmaceutique de la reproduction correspond à l’administration systématique d’hormones ou d’antibiotiques aux vaches à des fins de synchronisation des chaleurs, de synchronisation de l’ovulation, d’induction du vêlage, de prévention des infections utérines post partum. Le but est de faciliter la gestion de la reproduction dans les grands troupeaux ou, quelle que soit la taille de celui-ci, de diminuer la charge de travail de l’éleveur. Néanmoins, de tels systèmes n’améliorent pas systématiquement les performances de reproduction et leur intérêt économique reste à évaluer. Leur utilisation est également limitée en Europe par les réticences des consommateurs.

10. MOTS CLES

Synchronisation des chaleurs, pathologie post partum, hormones, antibiotiques, acceptabilité sociale.

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