

Pathologies of the puerperium in the cow

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1. In which context are we working ?

In 2013, European community counted 23,5 millions dairy cows which assume 24 % of the world production of cow's milk. By comparison, North and Central America produce 18 % of the world production. 44 % of the european cows were in Germany, France and Poland. In Europe, the total average milk production was 6627 kg of milk per cow and per year. Such average covers large differences between the different countries. For example, a difference of 3327 kgs is observed between danish cows (8667 kgs) and polish cows (5341 kgs). Such differences can

be explained by differences in genetic, nutritional resources and management including the capacities of the farmers and veterinarian to prevent and treat the different pathologies responsible of the wellbeing of the animals.

The aim of each farm is to produce a milk of quality. The recent suppression of milk quota in Europe has introduced a new goal. The new objective for the farmer is not necessarily to produce more milk per cow but to reduce as much as possible the costs of milk production. We can give two examples. The first concern the costs inherent to growing heifers. In Ontario (Canada), the costs (excluding interests and amortization) are respectively 1254 and 1451 Euros according the age of 24 and 28 months for first calving and respectively 9200 and 8700 kgs of milk during the first lactation. The second concern the economic consequences of uterine infections. In Europe such pathologies represent a loss of 1,4 billion Euros (Sheldon et al. 2009).

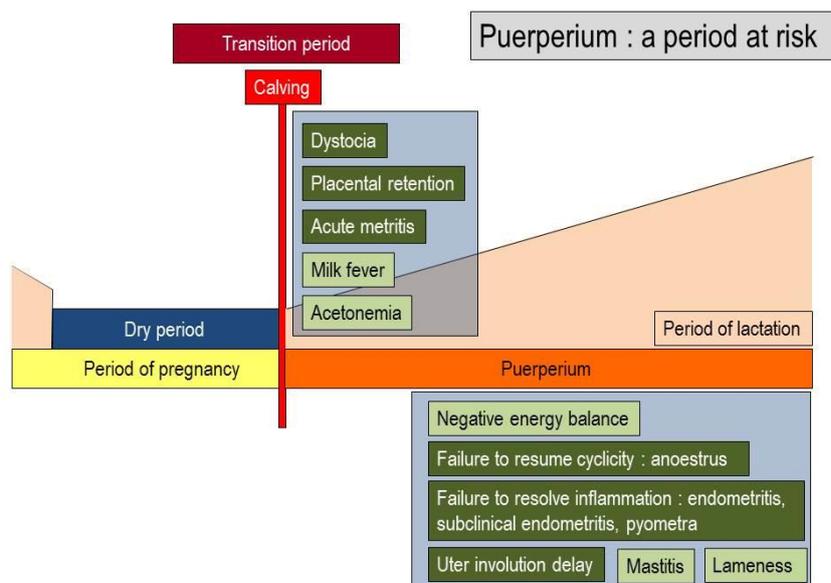
So this reduction of cost of milk production represent for the farmers and veterinarians a challenge even more difficult than the price of milk will continue to decrease during the next months according to what we can observe in different countries in Europe. In this context, the world market is not really a problem. It concerns only 7 % of the total milk production because most of the milk production is consumed in the countries where the milk is produced. The problem comes from the profit margins of the big companies.

2. Is puerperium important for cow reproductive performances ?

Puerperium can be defined as the period between calving and reproduction period (period between the first and the last insemination). This period can be assimilated to the waiting period i.e. the period between calving and the first insemination. The calving follows the end of pregnancy and in case of pluriparous cows the drying off period. Normally, for economic reasons, a new pregnancy needs to be observed as early 80 days after the previous calving. This goal can be obtained through a good preventive and if any curative management during day 20 and day 80 respectively before and after parturition. This period is often referred as the 100 days at risk for preproduction management.

For different reasons, puerperium is a high risk period for the fertility of the cow. Most of infectious, metabolic hormonal or locomotor pathologies appear during the period. Moreover, milk production increases during this period. At parturition and during the first days after, the dairy cow is at risk of dystocia, infectious diseases like placental retention or acute metritis, metabolic disease like milk fever or ketonemia. During the next two to seven weeks, the cow is exposed to a negative energy balance, to different uterine infectious disease like clinical and subclinical endometritis, pyometra, uterine involution delay, anestrus, mastitis, lameness or last but not least anestrus i.e. this failure to resume a cyclic ovarian activity (Figure 1).

Figure 1 : Pathologies of the puerperium according to the different periods



3. How to define these pathologies ?

To define as precisely as possible the different pathologies is important to use the best method of diagnosis, to make comparisons of prevalence of the different pathologies, to understand their risk factors and finally to evaluate the effect of their treatments.

1.1. *Dystocia*

The term dystocia from Greek *dys* meaning difficult and *tokos* meaning birth may be defined as calving difficulty resulting from prolonged spontaneous calving requiring a non surgical or a surgical (C-section) assistance to pull out the calf. Conversely, eutocia or normal calving may be defined as a spontaneous calving of normal duration. Taking the appearance of the amnion as the time of onset, calving (stage two) normally takes between 30 minutes and 4 hours with an average duration of 70 min being longer in heifers than in cows. Most of causes (70 %) of dystocia in cow are due to fetomaternal disproportion and abnormal presentations, positions or postures of the fetus (Mee et al. 2008).

1.2. *Placental retention*

In the cow, the placenta is expelled during the phase three of parturition. The retention of the placenta i.e. the fetal membranes is defined as the failure to expel the fetal membranes within 12, 24 or 48 h after calving. Most of the authors consider a period of 24 hours. The process of expulsion also called placental maturation begins some days before calving. According to the hormonal modifications but also the role played by the neutrophils, we can consider the placental retention as a physiological inflammatory process. There are a number of risk factors associated a modification of the natural inflammatory process including induced parturition, shortened gestation, abortion, twinning, dystocia, fetotomy, nutritional deficiencies like vitamin E, Se and carotene, infectious agents and immunosuppression (Beagley et al. 2010).

1.3. *Uterine involution and uterine involution delay.*

Uterine involution can be defined as a process of reduction in size of the uterus after calving due to loss of tissues (lochia), tissue repair and contractions. So different aspects can be distinguished. The first is anatomical aspect. The diameter, length and weight of the uterus decrease in 8 to 30 days due to the uterine contractions. Histologically, all the endometrium is eliminated and regenerated in 6 to 8 weeks after calving. Lochias are the main clinical sign. Their volume is between 500 to 2000 ml. They are visible until day 16 postpartum. They consist of necrotized uterine caruncles and endometrium, blood from ruptured umbilicus and of fetal fluids. Elimination of bacteriological content of the uterus represent one of the most important aspect of the uterine involution. The percentage of normally contaminated uterus decrease until day 50 i.e. during all the period of puerperium. Such evolution explain why it is not recommended to inseminate too early after calving and to respect at least a waiting period of 50 days. During the uterine involution the quantity of collagen is progressively reduced. Many hormonal changes can be seen during the involution period. Prostaglandins come mainly from the uterus. Some of them like PGF and leucotrienes promote the involution. Others like PGE, decreasing the immunity and activity of leucocytes as well as the contractions increase the risk of uterine involution delay. Other hormones like oestrogens and progesterone come from the ovary. The first are stimulating the uterine defense mechanism. It's not true for progesterone.

From a clinical point of view, uterine involution delay can be diagnosed by the palpation of one or both uterine horns with a diameter > 5 cm more than 30 days postcalving.

1.4. *Uterine infections*

Four kinds of uterine infections can be distinguished: puerperal/acute metritis, clinical and subclinical endometritis and pyometra.

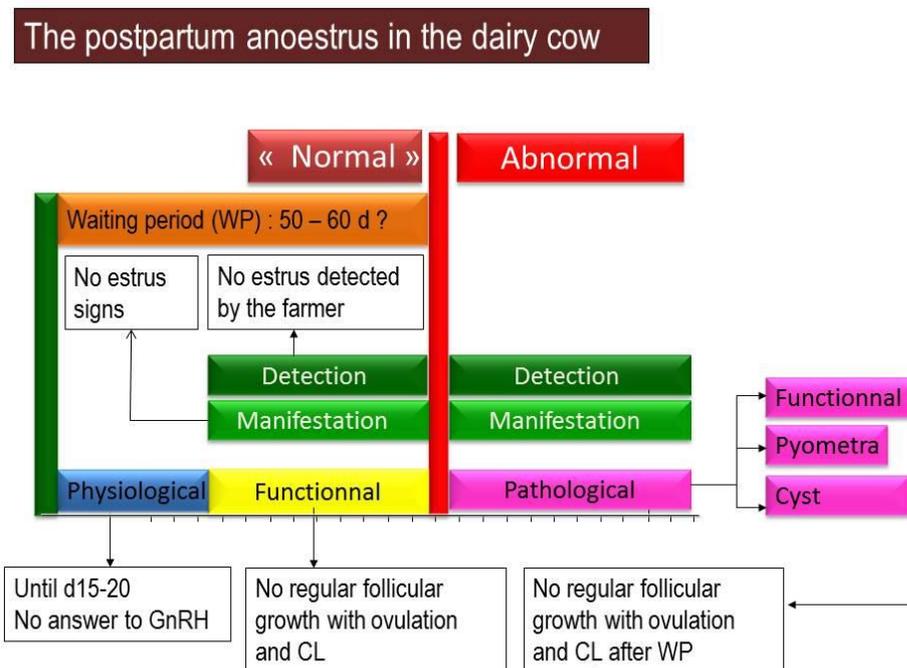
Acute puerperal metritis (APM) is defined as a uterine infection appearing during the first 21 days postpartum. The clinical signs are general (pyrexia more than 39.5°C, dullness, inappetence, anorexia, reduced milk yield) and / or local (Fetid red-brown watery uterine discharge, enlarged uterus, persistence of the uterine thrill). In absence of general signs, it's usual to call this uterine infection clinical metritis. Clinical endometritis results in local signs only visible after day 21. A uterine discharge can be seen and scored according to the amount of pus (pus more than 50 %, mucopus if 50 % of pus and 50 % of mucus and flakes of pus if < 50 % of pus. In case of subclinical endometritis, no clinical signs are visible. There is inflammation of endometrium without purulent material in the vagina. His diagnosis can be made counting the percentages of neutrophils in a sampling done into the uterine cavity. Pyometra is an accumulation of purulent or muco-purulent material in the uterus. The cervix is or not open. The uterus is enlarged. Such uterine infection usually appears after the beginning of cyclicity and increase of progesterone in the blood. Pyometra is often associated to a corpus luteum on the ovary (Sheldon et al. 2006).

1.5. The postpartum anestrus

Define the postpartum anestrus is relatively complex. The definition depends on the considered parameter: hormonal, behavioral or according to the follicular growth. Moreover absence of cyclicity can quite normal depending the time of postpartum taken in consideration. So it's possible to distinguished different kinds of postpartum anestrus before and after the normal waiting period considered of 50 to 60 days.

After calving and during 15 to 20 days, the ovaries of the cow can't be stimulated by an injection of the hypothalamic hormone called GnRH. It's a period of physiological anestrus. After this period and until the end of the normal waiting period, it's still possible to have any kind of regular follicular growth, ovulation and development of a corpus luteum. . In such situation we define this anestrus as functional. If such ovarian situation extends until after day 50 to 60 we are speaking on functional pathological anestrus. Pathological anestrus can results also from a pyometra or a cyst. In some situations, before and after the end of the normal waiting period, the cow becomes cycled, present an estrus but this estrus has been seen by the farmer. We call this anestrus detection anestrus. Finally, and mainly if the milk production is high (more than 40 l per day), the estrus signs can be low and not visible for the farmer: we call this anestrus a « manifestation » anestrus (Figure 2)

Figure 2 : the different postpartum anestrus



According to follicular and luteal ovarian activity four kinds of anestrus can be distinguished during the postpartum period (Peter et al. 2009).

In **anestrus type I** only recruited follicles with a diameter less than 8 mm can be observed by ultrasonography. At palpation such ovaries appears as smooth or granular. These follicles do not develop and therefore cannot reach the point of deviation. Such situation results from a

lack of luteinizing hormone (LH) needed for the final growth of the follicle. This lack is results from a severe undernutrition state. This situation should occur in less than 10% of cows in a herd. During **anestrus type II**, there was a follicular growth that continues until that stage of the deviation and the emergence of a dominant follicle. This growth is then followed by regression of the follicle. Two or three days later a new wave of growth can appear. Sometimes, nine waves can succeed before reaching ovulation. This lack of ovulation after follicular growth regularly is probably be due to an insufficient synthesis of estradiol by the follicle growth or a lack of his positive feedback on the release of luteinizing hormone. At palpation, it's quite possible to palpate a follicle without presence of cyst or corpus luteum. The **anestrus type III** is characterized by the presence of a follicular cyst. This cyst can continue to growth or can evolve to a luteinized follicular cyst. In presence of a cyst, follicular growth can be or not inhibited. In the **anestrus type IV**, the dominant follicle continues to grow until ovulation. This ovulation is followed by the development of a corpus luteum but corpus luteum does not regress and persist on the ovary. This lack of reduction involves an alteration of the luteolytic process. It is possible that the synthesis of estradiol by the follicle growth was not sufficient for inducing the formation of oxytocin receptors in endometrium and thus prevent and the pulsatile release of PGF2a. It is also possible that the synthesis of PGF2a was not sufficient because of extensive endometrial lesions induced by a pyometra. At palpation uterus is usually enlarged and the cervix is or not open. So pus can or not be seen by vaginoscopy.

4. What's the prevalence of these pathologies ?

The prevalence of these different pathologies are quite different according to the countries, the breed of cows, their management conditions, the stage of postpartum and also the definitions and methods used to make the diagnosis. Nevertheless, it's always interesting to have an idea of the prevalence because all these pathologies need to be investigated also at the herd level.

In dairy cattle, the prevalence of **dystocia** is between 3 and 23 % and 1.5 and 13.7 % in heifers and cows respectively. A threshold of 5 % can be considered as normal. From a large review of literature including 1,7 million cows and 2127 herds, the prevalence of **placental retention** is between 3 and 64,3 % the average being 8 %. This prevalence is twice as observed in beef cattle (3,9 % from 16.246 cows and 120 herds). From a study on 3.690 dairy and 6042 beef cows, we have observed the same prevalence of **uterine involution delay** between 31 and 50 days in both kinds of cows: 6 %. As mentioned by Sheldon (2009), the prevalence of **puerperal acute metritis, clinical, subclinical endometritis** and **pyometra** are respectively of 20 to 40 %, 15 to 20 %, 30 % and less than 5 %. According to an irish study (Fitzgerald 2013), the prevalence of uterine infections is decreasing during the weeks of postpartum in beef and dairy cattle, the highest prevalence being observed during the weeks 3 and 6. According to different studies conducted in different management systems, one cow out of five (20 %) don't present a regular cycling activity (**anestrus**) during the first two months of the postpartum. Moreover, according to a new-zealand study, large differences can be seen between herds. Considering studies with huge numbers of cows, the frequency of **cysts** is between 7 and 12 %. Also, we can consider that at the herd level, the threshold value can be 10 %.

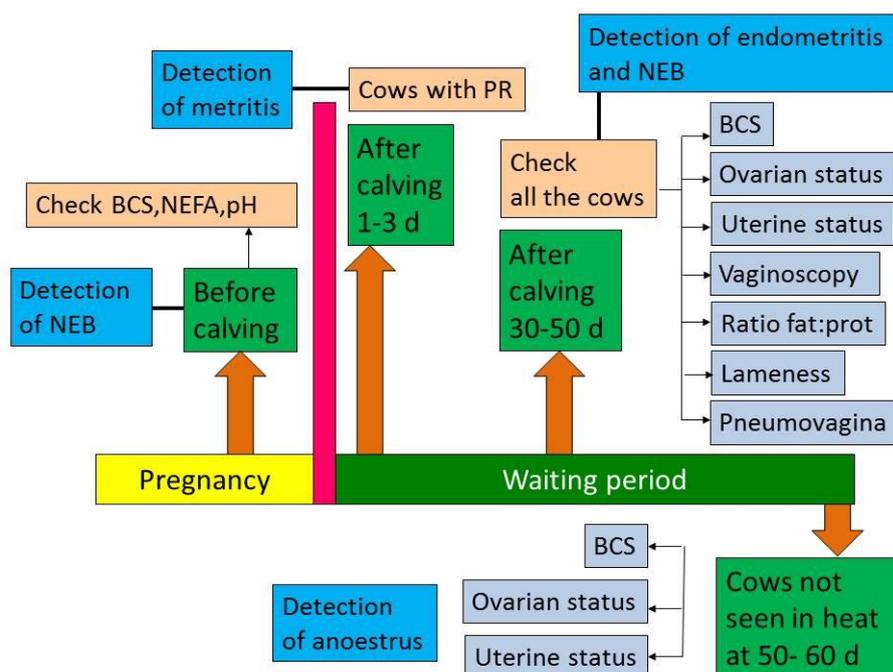
5. How to diagnose the pathologies of the puerperium ?

The farmer and the veterinarian has different tools. It's important to know how and what to see to detect for example dystocia or a placental retention. Thermometer is important to detect the cows suffering from puerperal metritis. It's recommended to take temperature on any cow presenting a placental retention. Vaginoscopy is still the best method to detect puerperal or clinical endometritis. A transrectal examination is very useful to make the diagnosis and to treat dystocia, placental retention, puerperal metritis, clinical endometritis and anestrus. A microscope is necessary to make the diagnosis of a subclinical endometritis. Ultrasound is sometimes required to make a differential diagnosis of the different anestrus.

6. When detect these pathologies ?

All the pathologies need to be detect as soon as possible. It's possible to organize different systematic examination of the cows at risk. Before calving, the cows can be checked for their body condition score and their concentration in non-esterified fatty acid (to detect a negative energy balance) or their pH of urine. During the first 1 to 3 days postpartum, any cow with a placental retention or hyperthermia ($> 39.5^{\circ}\text{C}$) need to be examined. Later after calving i.e. between 30 and 50 days postpartum, we need to realize a transrectal and vaginal examination to evaluate the ovarian, uterine and vaginal status. Locomotion score and body conditions score need also to be determined. Analyse of the ratio between fat and proteins in the milk could be also very useful to detect subclinical ketonemia and/or acidosis. If the cow has not been seen in heat during the first two months after calving, the palpation of the genital tract need to be done to determine the etiology of anestrus (Figure 3).

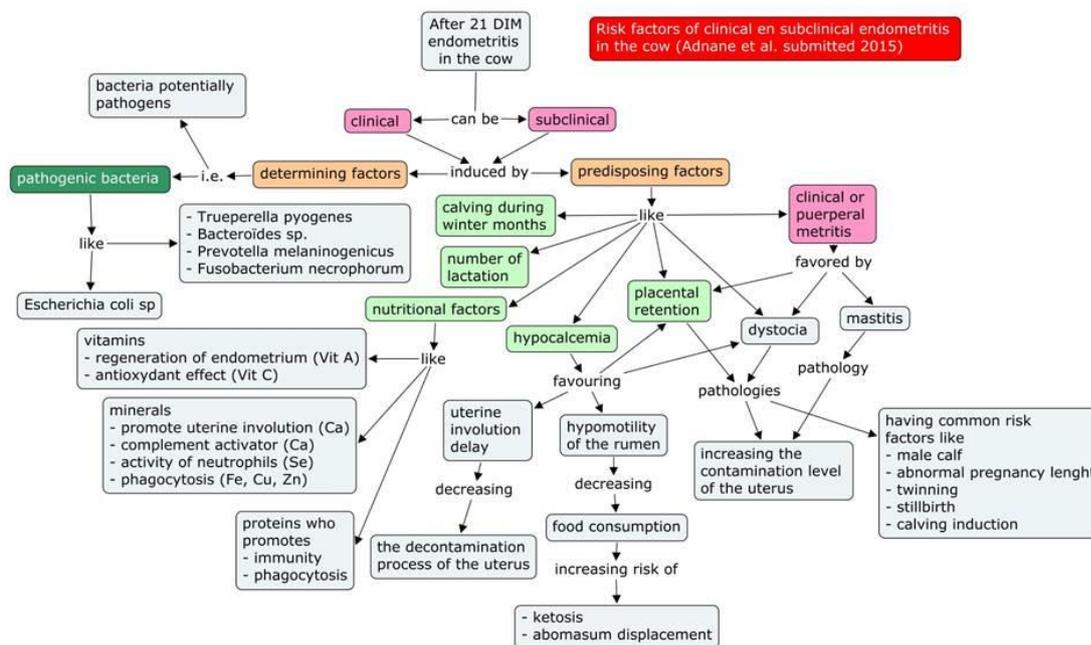
Figure 3 : Periods of identification of the postpartum ;pathologies



7. What kind of relations exist between these pathologies? The example of uterine infections.

As others pathologies, uterine infections depend on determining and predisposing factors. Bacteria are considered as determining factors. The bacteriology of the uterus after calving is very complex and different kind of bacteria can be found. Some of them are contaminant, other can become pathogens and finally we can detect bacteria really pathogen like *E.coli*, *Trueperella pyogenes*, *Prevotella melanogenicus* or *Fusobacterium necrophorum*. Different types of predisposing factors can influence the possibility for the cow to develop early or latter an uterine infection. Calving during the winter months increase the infection pressure. The risk of uterine infection decreases with the number of lactation, primiparous cows being more at risk of dystocia. Nutritional factors like vitamins, minerals or proteins have been involved in uterine infections. Hypocalcaemia is related to nutrition. Such clinical or subclinical pathology promotes uterine involution delay and so decreases the decontamination process of the uterus; Hypocalcaemia has also been involved in hypomotility of the rumen. As consequence, food consumption is decreased and the risk of ketonemia and abomasum displacement are increased. Moreover hypocalcaemia can also promotes dystocia and placental retention. Puerperal metritis is a predisposing factor for a clinical and subclinical endometritis. The pathology result from dystocia, placental retention or mastitis, all conditions promoting the contamination level of the uterus. Dystocia and placental retention have some commons predisposing factors like male calf, abnormal pregnancy length, twinning, still birth or calving induction (Leblanc 2014). All the postpartum pathologies interact with one another (Figure 4). Different epidemiological studies have enlightened the relationship (odds ratio) between different puerperal diseases and uterine infections. For example and according to different studies these odds ratio are respectively 2.3 (primiparous cows) 0.9 to 1.7 (multiparous cows), 2.1 to 4.9 (dystocia), 6.3 to 7.5 (stillbirth), 1.8 to 2.4 (male offspring), 2.2 to 6.6 (twinning), 4.7 to 27.7 (placental retention), 0.5 to 3.8 (ketosis), 1.8 to 3.5 (milk fever), 3.6 to 4.7 (displaced abomasum) (Adnane et al. 2015).

Figure 4 : Relationships between the postpartum pathologies and the uterine infection



8. How to treat these pathologies ?

Therapeutical strategies will depend on the importance of the problem. If the problem is individual, it's important to make the right diagnosis using the best method. Different usual recommendations can be done. If the herd is concerned (see the prevalences of the different pathologies), it becomes very important to take in consideration the different risk factors. It's impossible to solve the problem of puerperal metritis if the problem of placental retention has not been solved. In such case it would be necessary to combine a preventive and a curative approach.

Concerning the uterine infections, it's necessary to make some preliminary observations and/or recommendations (Bradford et al. 2014). (1) Uterine infections are inflammation (including placental retention) and inflammation is a defense mechanism for the cow, (2) during the first weeks postpartum uterine cavity is contaminated by a quite large number of bacterial species, (3) few data on in vitro susceptibilities of bacteria isolated from the bovine uterus are available, (4) selection of an antibiotic is usually made on an empirical basis, (5) under field conditions, bacteriological sampling of the uterus is usually not feasible and (6) the policy regarding the use of antibiotics in general and particularly cephalosporins are quite different between the countries (Pyorala et al. 2014).

Concerning the treatment of **placental retention**, no effect or harmful effect has been observed after treatment by manual removal associated or not with local antibiotics (bolus or infusion) or with parenteral antibiotics. There is no effect at all of oxytocic agents (oxytocin, carbetocin,

PGF2a). So we can recommend to make a follow-up of temperature and clinical condition and to treat only cows who develop puerperal metritis (Beagley et al. 2010).

Classically, **puerperal metritis** (local and systemic signs of illness) and **clinical metritis** (puerperal metritis without systemic illness) are treated with penicilline, ampicilline and ceftiofur associated or not with intrauterine injection of oxytetracycline, ampicillin or cloxacillin. Injection of PGF2a has no effect. According to a recent review (Haimerl and Heuwieser 2014), we need to a standard gold method, to make more research about selfcure, to test alternative methods of treatment and to defined better the ratio cost-benefits. Some news treatment have been proposed. They aim to modulate the inflammatory reaction using non steroidal anti-inflammatory (NSAI) drugs like flunixin (increase the involution of the uterus if metritis), salicylates (given in early lactation, increase of milk production), meloxicam (decrease the risk of culling if mastitis) and carprofen (increase time spent eating after dystocia). Such NSAID drugs can have some negative effects like the suppression of inflammation mechanism (parturition induction and placenta maturation) and the presence of residues (milk removal for 3 to 5 days). Some trials with LPS vaccination or bioactive fatty acid (flaxseed) and anti-oxidants (Vit E, Se) to neutralize ROS and decrease inflammation have also been done (Bradford et al. 2014).

Many antimicrobial compounds used for local treatment of **clinical endometritis** (tetracycline, penicillin, cephalosporin, chloramphenicol, iodine, gentamycine, spectinomycin, sulphonamides, nitrofurazone, chlorhexidine). Such antibiotics are no longer approved and their efficacy has not been demonstrated. As far as we know, cephalosporin (1st generation cephalosporin) is an exception and need to be recommended because ceftiofur (3rd generation cephalosporin) parentally used has no effect and is a public health problem.

There is no specific treatment for **uterine involution delay** except to control the risk factors. (puerperal metritis, dystocia, placental retention, milk fever).

The treatments of **postpartum anoestrus** can be considered in two aspects. The first concerns the non cycled animals and the second the cycled animals.

Some general recommendations need to be taken in account. (1) It's necessary to make a good differential diagnosis of the different post-partum anoestrus with anamneses, manual palpation, echography, BCS and vaginoscopy. (2) It's unnecessary to treat with hormones any anoestrus (except pyometra) during the first 50 to 60 days post-partum. (3) Again, it's important to detect and to treat as soon as possible the uterine infections (including pyometra). (4) we need to avoid to treat with hormones, the cows having a BCS lower than 2.5. The effects of the different hormones are quite different. So PGF2a can induce (one cow) or synchronize (several cows) oestrus if the heifer/cow has a corpus luteum. The progestogens (progesterone given vaginally with CIDR Zoetis or PRID Delta Ceva), norgestomet) can induce (one cow) or synchronize (several cows) oestrus if the heifer/cow in absence of corpus luteum and GnRH can induce (one cow) or synchronize (several cows) ovulations if the heifer or cow has a dominant follicle i.e. a follicle with a diameter > 8-10 mm.

Some general recipes can be proposed according to the type of anestrus in non cycled animals. There is no hormonal treatment for anestrus type I. We need try to increase the body condition score. Anestrus type II can be treated with progestogens associated or not with GnRH or G (Equine Chorionic Gonadotropin). Anestrus type III (ovarian cysts) will be treated with PGF2a in case of luteal cyst) and by GnRH, hCG, or progestagens in case of follicular cyst. Anestrus type IV (pyometra) will be treated with PGF2a.

Many different treatments have been proposed to induce and / or to synchronise cycled animals (Hanzen and Boudry 2003). All of them are using the PGF2a associated or not to GnRH or progestagens and sometimes to esters of oestradiol (elsewhere than in Europe). One of the most known is the Ovsynch protocol who associates GnRH (Day 0) , PGF2a (Day 7) and GnRH (Day 9). Before using any treatment with PGF2a, be sure the heifer/cow has a corpus luteum bigger than 2 cm (PGF2a has effect during metoestrus, prooestrus or estrus), and be sure that the cow is not pregnant (between day 6 and 150). Moreover, earlier PGF2a is injected during diestrus, smaller is interval between injection and beginning of estrus. Usually, the use of PGF2a (with or without GnRH) don't increase the fertility but reduce the waiting period. It's necessary to adopt a good policy of insemination : timed artificial insemination (TAI) or insemination done after an observed estrus. Finally take also in account the costs of labor and hormone administration when selecting this form of reproductive technology for routine use.

9. Conclusion

Key management regarding the link between the pathologies is of preventive nature. Modern research stresses the management of subclinical energetic and mineral metabolism before calving. The new "frontier" in reproduction management could be the difficult equation solving between health, ingestion capability and milk production. A trend in research is the inflammatory approach to these pathologies to understand to underlying mechanisms.

There are many ways to prevent natural causes of uterine disease risk factors as insemination choice, specifically on heifers. As veterinarian, we have a lot of possible treatments for uterine diseases, but research shows the relative small efficacy of that therapeutics. Yet, a precise management of the days post-partum through reproduction follow ups and early echography is still the central role of the veterinarian to enhance diseased animal screening. In peculiar when time to action is critical concerning clinical and subclinical endometritis risk.

One take home message is that insemination choice, energy balance is our prepartum keys, that could be standardised through procedures. Another could be that early management of puerperal metritis, and ketonemia could be the key for postpartum prevention.

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