Potential Impact of Viral Diseases on Conception Rates in Cattle

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Take Home Messages

- Many viral diseases are endemic in cattle populations. Their impact on production losses is established, but effects on fertility are often underestimated.
- Viral infections can disturb normal ovarian function, inhibit early embryo development and cause abortions and fetal malformations later in pregnancy. They also suppress immunity and so increase the risk of cows developing uterine disease due to bacterial infections after calving.
- Three common viruses—BVDV, BoHV-1 and BoHV-4— all reduce conception rates.
- Knowing which viruses are present in a herd and taking proactive measures to reduce the risk of viral infections through vaccination and good biosecurity measures should improve general herd fertility.

Introduction

Many viral diseases remain prevalent in the cattle population worldwide while new ones threaten to emerge. Some of these diseases are controlled in different countries through various vaccination and slaughter programs, but trade globalization, increasing herd size, and environmental change have all contributed to their spread. They are known to cause major financial losses to the dairy industry (Richter et al., 2017). With respect to fertility, the ability of some viruses to cause abortions and fetal malformations is the most evident manifestation and has received the most attention (Ali et al., 2012). The outcome will, however, depend on the stage of pregnancy when the initial infection occurs. Conception rates may be reduced and this in turn will increase the risk of culling through failure to conceive in a timely fashion. These effects are much harder to quantify because many other factors relating to the health and management of the cows are also influential, so it is hard to separate out their respective contributions. This means that the potential impact of viral disease on fertility is generally underestimated. This paper describes some of the ways by which viruses can reduce conception rates using three common viruses found in cattle as examples: bovine viral diarrhea virus (BVDV), bovine herpes virus 1 (BoHV-1) and bovine herpes virus 4 (BoHV-4). These have varied mechanisms of action and are all currently endemic in the Canadian cattle population.

Factors Affecting Reproductive Efficiency

Many factors affect the reproductive performance of individual cows and consequently herd fertility. These can be categorized under the following three broad headings: 1) the interval from calving to resumption of ovulation and regular estrous cycles, 2) estrous detection efficiency and submission rate, and 3) conception rate following service. In general, about 80% of dairy cows ovulate for the first time within the first 4 weeks after calving, with around 10% of cows remaining acyclic at 6 weeks (Wathes et al., 2007). The main cause of prolonged anestrum is negative energy balance (NEB), which impacts the ability of the ovary to grow and ovulate a mature dominant follicle. Other events in the peripartum period such as an abnormal calving or early disease episodes (e.g., mastitis, metritis, displaced abomasum) are also influential.

Once cycles have resumed, the subsequent pattern of estrous cycles can be monitored through the use of milk progesterone profiles (Wathes et al., 2007). If a cow has ovulated within 4 weeks of calving, she can experience one or two cycles before she needs to be bred, which increases the likelihood that she will conceive at the appropriate time. However, only about half of high yielding dairy cows achieve this normal pattern. Apart from a delayed resumption of cyclicity, some cows develop a persistent corpus luteum. This occurs more often in multiparous cows and is particularly associated with uterine disease. Opsomer et al. (2000) reported incidences of 15% in first parity cows, 24% in parities two and three, and 32% in parities ≥ 4. Other cows (5-10%) experience an irregular pattern of fluctuating progesterone levels, which may be associated with the development of luteinized cysts (Opsomer et al., 2000; Wathes et al., 2007). All of these irregularities in cycle pattern make reliable heat detection more difficult. Because they reflect underlying issues relating to the health and physiology of the individual cow, they will also affect the likelihood of a successful response to a timed insemination regime.

The actual conception rate is determined by the initial fertilization rate minus any subsequent losses due to death of the embryo (Table 1). Providing that adequate numbers of spermatozoa are used from bulls with high fertility and that cows are inseminated at the correct stage of the cycle, then available evidence indicates that fertilization rates are usually around 90%. Calving rates to a particular service are, however, much lower and this is largely attributable to high rates of early embryo loss (Diskin et al., 2016; Table 1). Calving rates to a particular service of around 65% are achievable in dairy heifers, reducing to 30% or less in high-producing cows. If fertilization rates are 90%, this implies that around 35–70% of all potential pregnancies do not result in birth of a live calf. Of these, approximately 40% of bovine embryos die in the first 3 weeks after service or insemination, with cows returning to estrus at the normal time at about 21–24 days. A further 5–25% of embryos are lost between days 24–60 of gestation. Greater loss rates at this later stage have been associated with higher levels of milk production, episodes of mastitis or high ambient temperature. The later embryo losses are numerically fewer than the earlier ones, but they have a greater impact on the fate of the individual cow. By the time they are detected it may be too long after calving to rebreed the animal, so many are culled. Once the pregnancy progresses beyond two months then abortion rates are usually quite low, around 5%. Abortions are often associated with specific diseases that include opportunistic bacterial infections (e.g., *Arcanobacterium pyogenes*), zoonotic bacteria (e.g., *Leptospira spp*), fungal infections (e.g., *Aspergillus fumigatus*), protozoa (e.g., *Neospora caninum*) and viral infections (e.g., BVDV, infectious bovine rhinotracheitis). However, in over half of cases submitted for diagnosis no infectious agents are identified (Givens and Marley, 2008).

Table 1. Summary of pregnancy losses in cattle from insemination until calving

Stage of pregnancy	Reason	Reported range of lost pregnancies	Number of cows still pregnant	
			Worst case	Best case
Insemination of dam			100	100
Fertilization of oocyte	Fertilization failure, wrong time AI	0-20%	80	100
0-24 days post AI	Early embryo mortality	30-50%	40	70
25-60 days post AI	Late embryo mortality	5-25%	30	67
61 days until term	Abortion	3-10%	27	64

▪ Establishment of Pregnancy

Following a successful fertilization, the embryo should enter the uterus on days 4–6 post mating and then form a spherical blastocyst, initially surrounded by the zona pellucida that enclosed the original oocyte.

The blastocyst then hatches out of the zona pellucida on about day 8 and develops into an ovoid and then tubular conceptus that begins to elongate on around day 15 into a filamentous form which should extend to occupy the entire length of the uterine horn. This elongation is critical to enable production of sufficient interferon tau (IFNT), which is synthesised by the outer trophectodermal layer of the conceptus from around day 8 (Dorniak et al., 2013). Interferon tau is the pregnancy recognition signal in cattle and is required to prevent regression of the corpus luteum and the continued production of the pregnancy hormone progesterone. It also induces the endometrium to produce a large number of other molecules that act to remodel the endometrium to a receptive environment and promote further development of the conceptus. This is essential to enable successful implantation and subsequent formation of the placenta.

It can be seen from the above that anything which perturbs the early stages of embryo development will also reduce reproductive efficiency. Some embryos fail to develop normally because of genetic abnormalities that were present from fertilization. The environment within the cow's reproductive tract is equally important because it must provide everything required to support blastocyst growth (Dorniak et al., 2013). The uterine environment is strongly influenced by a variety of factors that include the ovarian steroid hormones estradiol-17β and progesterone, the nutritional status of the cow, and inflammatory agents including prostaglandins and cytokines. Amongst these, the timing of the rise in progesterone after ovulation is of key importance, while any infectious diseases contracted earlier in the postpartum period, particularly those causing endometritis, can result in long term inflammatory changes in the endometrium.

Specific examples with references are given below, but in broad terms viral diseases influence many of the processes outlined that are required to achieve a successful conception and establish pregnancy. Fever during the follicular stage of the estrous cycle can inhibit ovulation via actions at the level of the brain. Viruses can also affect the ovary directly, inhibiting follicular development and steroid hormone production. Based on in vitro culture systems, direct effects on the early stages of embryo development are sometimes apparent although viruses may be unable to cross an intact zona pellucida. Many viruses have, however, evolved mechanisms to evade or suppress the normal immune mechanisms that the host uses to repress them in order to promote their own survival. Immunosuppression can then make the animal more susceptible to any other disease agents to which it is exposed. Some of these immune mechanisms are also essential components of pregnancy recognition and implantation, so these may also be prevented.

▪ Examples of Viral Diseases Affecting Fertility

Bovine Viral Diarrhea Virus (BVDV)

BVDV is a pestivirus belonging to the family *Flaviviridae*, comprising a single-stranded, positive sense RNA genome that is classified by sequence differences as type 1 or 2 (BVDV-1 or -2). It is endemic in many countries, with a prevalence of 40–90% of individual cattle and 28–66% of herds and is known to cause major economic losses (Richter et al., 2017). It exists as either cytopathogenic (cp) or non-cytopathogenic (ncp) biotypes, with the ncp biotype causing the majority of field losses (Ridpath, 2003). A third atypical pestivirus, BVDV-3, is also in circulation.

If a pregnant cow becomes infected with ncp BVDV between about 1 to 4 months of gestation, before the fetus develops its own immune competence, the result is either early embryonic death(abortion) or birth of an immunotolerant calf that is persistently infected with BVDV. Persistently infected calves shed virus continuously, so if they are undetected at birth or are purchased, they are a major source of infection within a herd. Those herd members that subsequently become infected acutely should be able to eliminate the virus within 10–14 days. During this period, they transmit virus to other animals they are in contact with, mainly via secretions from the mouth and nose, but direct transmission to the reproductive tract via semen from an infected bull or embryo transfer is also possible. Some animals carry transmissible virus for several months after they have apparently recovered. During such an acute infection BVDV causes immunosuppression through its ability to inhibit production of type 1 interferons (IFN), so delaying the host's responses and enabling the virus to complete its own replication cycle

(Oguejiofor et al., 2019).

With respect to fertility, the effects on abortion, fetal deformity and birth of persistently infected calves are the best known consequences and a meta-analysis of vaccinated cows found a reduction of nearly 45% in the abortion rate and of 85% in fetal infection in comparison with unvaccinated cohorts (Newcomer et al., 2015). BVDV can, however, impact on most stages of the reproductive cycle, depending on when an individual cow or heifer becomes infected. A number of primary studies using either experimental infections of naïve animals or field reports have attempted to quantify conception rates and have reported reductions of up to 44% if an animal develops an acute infection in an approximate 4-week window covering the period immediately before or after insemination (Fray et al., 2000). No such effect was found when persistently infected animals were introduced to naïve heifers 7 weeks before breeding, presumably because they then had sufficient time to recover (Rodning et al., 2012). Vaccination against BVDV increased the likelihood of cows becoming pregnant by about 5% (Newcomer et al., 2015).

BVDV infections can reduce fertility via effects on the ovary, uterus and early embryo. The ovaries may become inflamed, affecting follicular development including growth of the dominant follicles. The timing of ovulation can be delayed and there may be a longer interval from ovulation to the time of the subsequent progesterone rise followed by reduced luteal progesterone production. Several studies have investigated the effects of BVDV infection on early embryo development in vitro. The effects were dependent on the strain used (Oguejiofor et al., 2019). In general, infection with ncp BVDV type-1 or -2 did not adversely affect embryo development but cp BVDV caused cell death when the zona pellucida was not present, while BVDV-3 reduced both cleavage and blastocyst rates. From this it appears that BVDV type-1 present in the uterus probably does not have a direct negative impact on the development of embryos prior to hatching because the zona pellucida is protective. The risk of transmission of BVDV to host cows via embryo transfer is also low as long as correct washing procedures (as recommended by International Embryo Transfer Society guidelines) are applied.

Virus can be found in the uterus for at least 3 weeks after initial infection and there is good evidence that this may reduce fertility in two ways (Oguejiofor et al., 2019). Firstly, the fact that BVDV causes immunosuppression will increase the likelihood that the cow may develop endometritis if she becomes infected with BVDV in the peripartum period. This is already a high-risk time because the uterus is normally colonized with many bacterial species following calving. Healthy cows should be able to respond rapidly using local immune defence systems that involve epithelial and stromal cells together with specialized white blood cells that are also present in the endometrium. If this early response is sufficient, then the bacterial infections can be cleared and the cow will not go on to develop uterine disease.

Up to 50% of postpartum dairy cows do, however, develop metritis, endometritis and/or cervicitis, which may in turn result in long term chronic inflammation of the uterine wall that continues to have adverse effects on the intrauterine environment even after the initial infection has passed. We have shown using in vitro culture techniques that experimental infection of endometrial cells with ncp BVDV markedly reduced their ability to mount an immune response to a challenge with the bacterial wall component lipopolysaccharide. Amongst the changes observed, the ratio of prostaglandin produced by the endometrium switched from the luteolysin $PGF_{2\alpha}$ to more PGE_2 (Oguejiofor et al., 2019). In the reproductive tract $PGF_{2\alpha}$ acts as an immune enhancer while PGE_2 is an immune suppressor and also helps to maintain the corpus luteum. The relative increase in PGE_2 would therefore not only promote inflammatory changes within the endometrium itself but would also increase the likelihood of a cow developing a persistent corpus luteum, which is one of the detrimental consequences associated with uterine disease.

The second way in which BVDV can reduce conception rates involves its ability to inhibit immune pathways. As mentioned above, a normal response to an infection includes increased local production of type 1 interferons. These then act through interferon receptors in the endometrium to up-regulate many interferon stimulated genes that play an important part in local defence mechanisms. However, the cow uses IFNT produced by the conceptus to signal that she is pregnant. IFNT is also a type 1 interferon that acts through the same interferon receptors as those involved with the normal immune response to induce local changes in the endometrium. In the case of IFNT these include remodelling of the uterine wall, increased blood flow, production of uterine secretions and alteration of the local immune response to prevent the dam from rejecting the conceptus (which is genetically dissimilar to her own tissues). All of these steps are essential to promote sufficient nutrient supply to the pre-attachment conceptus and then to enable it to establish a functional placenta. Again, using in vitro techniques, we have shown that endometrial cells infected with ncp BVDV have not only a reduced ability to synthesize type 1 interferons, but their ability to respond to IFNT by production of interferon stimulated genes is also seriously impaired (Oguejiofor et al., 2019). This is likely to be the main mechanism whereby BVDV infection around the time of estrus or in the early luteal phase can prevent the successful establishment of a pregnancy.

Bovine herpesvirus-1 (BoHV-1)

Bovine herpesvirus-1 is a herpes virus that also impacts on fertility. Following an initial infection, the body is usually unable to eliminate members of the *Herpesviridae* family completely and the viruses are able to remain in an inactive, latent state in some parts of the body including neural tissue and macrophages. The virus can then be reactivated in times of stress, or if the body is faced with a subsequent disease challenge. In the case of BoHV-1, it initially causes infectious bovine rhinotracheitis (IBR), an acute and highly contagious inflammation of the upper respiratory tract that is endemic in many parts of the world, including the UK and Canada. Bovine respiratory disease (BRD) is the main cause of mortality and morbidity in dairy calves between 1–5 months of age, and BoHV-1 is one of a variety of pathogens that contribute to this (Johnson et al., 2012). BoHV-1 can also cause conjunctivitis, encephalitis and abortion. In those animals surviving an initial BoHV-1 infection, latent virus can be reactivated by glucocorticoids (Rock et al., 1992). Because glucocorticoid levels increase as part of the normal parturition mechanism and the cow is subsequently likely to suffer from both bacterial infections and negative energy balance, the postpartum period is clearly a high-risk time for the virus to reactivate.

BRD is extremely common in dairy herds, with numerous epidemiology studies showing that up to 46% of calves are affected (Johnson et al., 2011). The consequences of this have been reviewed (Wathes et al., 2014). Surviving heifers have reduced growth rates, which in turn delay the age at which they are ready to be bred and so the age at first calving. For those affected in their first 3 months of life, first calving was delayed by around 6 months and subsequent calving intervals were increased by 12%. The most severely affected animals, which experienced four episodes of BRD before calving, were 1.9 times less likely to complete their first lactation compared with their healthy compatriots. Because BRD is associated with a variety of infectious agents, not all cases will be associated with BoHV-1 infection. However, the importance of BoHV-1 in these effects on fertility was supported by a study of seasonally calving Irish herds that measured antibodies against BoHV-1 in bulk milk tanks and found that the 3-week calving rate was significantly lower in herds that tested positive compared with BoHV-1 negative herds (Sayers, 2017). Further epidemiology studies in Ethiopia found that cows that were seropositive for BoHV-1 had significantly higher rates of uterine infection and more retained fetal membranes than cows that tested negative (Asmare et al., 2018).

Further support for the role of BoHV-1 in reducing fertility has come from a number of studies that investigated the effects of treating cattle with modified live IBR vaccine at estrus or within the subsequent 4 weeks (Chase et al., 2017). The main effects noticed involved the ovary, which developed regions of necrosis affecting both follicles and the corpus luteum. Vaccination at estrus was followed by reductions in circulating progesterone levels and conception rates. The manufacturer therefore recommends that the vaccine be given one month before breeding. To our knowledge, possible actions of BoHV-1 on the immune function of the uterus, such as those described for BVDV, have not been investigated to date, but would not be unexpected.

Bovine herpesvirus-4 (BoHV-4)

Bovine herpesvirus-4 is another herpes virus that is highly prevalent in some dairy herds and also remains latent in the body following initial infection in several cell types including macrophages (Gagnon et al., 2017). In common with BoHV-1, there is in vitro evidence that BoHV-4 can be reactivated by glucocorticoids. In addition, in vivo evidence measuring seroconversion rates has shown that it can reactivate during the peripartum period. BoHV-4 infects the uterus and its presence there has been associated with both metritis and endometritis (Donofrio et al., 2008). Evidence that it can reduce fertility includes studies showing that BoHV-4 positive cows were less likely to be inseminated in the first 80 days postpartum, they required more services per conception, and they had a reduced likelihood of conceiving again within 200 days of calving in comparison with uninfected cows (Chastant-Maillard, 2015).

The causal role of BoHV-4 in uterine disease is somewhat unclear as it can also be found in cows that did not have uterine infection and its presence in the uterus is usually associated with well-recognized bacterial pathogens including *Trueperella pyogenes* and *Escherichia coli* (Klamminger et al., 2017). Available evidence now supports the view that BoHV-4 acts as a co-factor with such bacterial pathogens to increase the likelihood that an infected animal will develop endometritis (Donofrio et al., 2008). It does this by increasing local production of the chemokine IL8, which then acts to attract immune cell migration into the uterus and activate a variety of inflammatory cytokines including interleukin (IL)1, IL8 and tumour necrosis factor alpha. In common with BVDV, the presence of BoHV-4 in the uterus therefore alters the normal immune response to bacterial infection. Unlike ncp BVD however, BoHV-4 is cytopathic, and can kill endometrial epithelial and stromal cells. Because the uterine epithelium is normally protective, this increases the vulnerability of the underlying stromal cells to direct attack by intra-uterine pathogens.

▪ Evidence for the Importance of Viral Diseases in Dairy Cow Fertility

In summary, the three viruses used here as examples are all in circulation in Canadian dairy herds. An acute ncp BVDV infection experienced during the breeding period can reduce cow fertility by causing estrous cycle irregularities, early embryo mortality and immunosuppression. Later infections will increase abortion rates or result in birth of a persistently infected calf. Many dairy calves experience BRD, and this is often associated with BoHV-1 infection. BRD slows growth, delays first calving and increases the subsequent likelihood of culling. There is good evidence that BoHV-1 impairs ovarian function and is associated with uterine infection, lower conception rates and abortion. Furthermore, latent virus remains present following the initial infection and can be reactivated if the animal is stressed. BoHV-4 infections alone are probably insufficient to cause clinical uterine disease, but if the virus is already present then it can also be reactivated from latency following calving and then act together with bacterial pathogens to disrupt the normal immune response, so increasing the risk of endometritis and delaying uterine repair mechanisms (Figure 1).

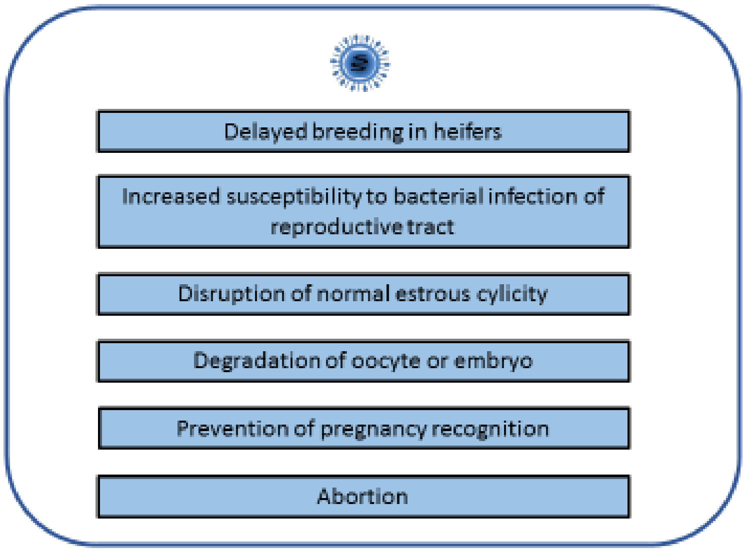

Figure 1: Summary of possible ways in which viral diseases reduce fertility in dairy cows

These three examples show that some common viruses can act through a diverse range of mechanisms to have adverse effects on the ovary, endometrium and the conceptus, so reducing fertility. Their presence in the herd may be identified if there is an issue with high rates of abortion or fetal abnormalities. Nevertheless, they are not usually top of the list of considerations when herds are experiencing suboptimal conception rates. In practice, fertility rates in the field are influenced by many factors that each make a small contribution. It is often hard to identify their relative impact because many potentially relevant factors are not recorded in an easily accessible format to link to the success of a particular insemination. For example, previous disease and vaccination history, changes in feed constituents and the current metabolic status of individual cows are all influential.

In addition to the work cited above, we have recently acquired new evidence that viral disease may indeed play an influential role on conception rates. Peripheral blood is becoming widely used to determine gene expression profiles associated with a variety of infectious and non-infectious diseases of both humans and domestic livestock. Such blood contains a population of white blood cells that circulate between disease sites and lymphoid organs in the body. As part of a recent EU sponsored study, GplusE (www.gpluse.eu), we acquired blood samples from 176 multiparous Holstein cows from six herds, each based in a different country. These samples were taken at 2 weeks after calving, when cows are often in a state of negative energy balance. We then measured both the circulating metabolic hormone insulin-like growth factor-1 (IGF-1) and the global gene expression profile in the white blood cells, using the technique of RNA sequencing. We have shown previously that the IGF-1 concentration at this time is strongly related to the energy balance status and is also highly predictive of future fertility in that lactation. We found that multiparous cows whose circulating IGF-I concentrations exceeded 25 ng/mL in the week after calving were 11 times more likely to conceive to first service than those with lower IGF-1 concentrations (Wathes et al., 2007). In the recent GplusE study we then used a technique of data analysis known as weighted correlation network analysis to identify clusters of genes whose expression pattern in white blood cells was highly correlated both with each other and also with the circulating IGF-1 concentration. This analysis showed that the genes in the cluster that had the strongest overall negative relationship with the IGF-1 concentration are known to be important in innate immune responses, in particular relating to viral infection. As outlined above, the IFN system represents the first line of defense against a wide range of viruses, with the rise in IFN activating antiviral responses using at least five main effector pathways. We found that key genes involved in each of these five pathways were up-regulated in cows in which the circulating IGF-1 concentration was low. This evidence is strongly indicative that such cows were responding to a viral infection at this time, although none was specifically identified in their clinical records. We believe that the most likely explanation for these observations is that a pre-existing but latent virus had been reactivated in the peripartum period in those animals with a low energy balance status. This would then represent a chicken-and-egg situation, as mounting an effective immune response is energetically demanding and so would further deplete the available body reserves.

▪ Conclusion

A wide variety of viral diseases are present in cattle populations. Although they are acknowledged to cause major production and economic losses, few have been controlled effectively at a global scale and there is always a real danger that new strains or completely new diseases may emerge. Detecting these requires a vigilant screening process combined with robust epidemiological studies to inform both national and international animal health policies. Applying rigorous quarantine procedures can reduce the risk of disease spread. This applies not only between countries but also at a farm level when any newly acquired animals are introduced into a naïve herd. This precaution will however be ineffective against some vector borne diseases such as Schmallenberg and Bluetongue virus. Various schemes have been implemented to incentivize farmers to increase their use of regular testing and appropriate vaccination. Disease monitoring may in future benefit from the development of more rapid and reliable diagnostic procedures. Amongst other benefits, reducing the prevalence of viral diseases in dairy herds should improve conception rates and increase cow longevity.

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