Impact of endemic viral disease on cattle fertility

D Claire Wathes, BSc, PhD, DSc.
Royal Veterinary College, University of London
UK

dcwathes@rvc.ac.uk

Many viral diseases are endemic in cattle populations worldwide, causing major financial losses to the industry. Their potential impact on fertility is, however, generally underestimated and the main mechanisms of action are often unclear. The ability of many viruses to cross the placenta and cause abortions and fetal malformations is well understood but there is additional evidence that viral infections of cows are reflected in reduced conception rates. These effects are, however, highly dependent on the time when an individual animal first contracts the disease and are less easy to quantify. This talk will cover evidence relating to five examples: bovine viral diarrhoea virus (BVDV), bovine herpes virus-1 and -4 (BHV-1, BHV-4), Schmallenberg virus (SBV) and Bluetongue virus (BTV)., BVDV has been the most widely studied with respect to fertility, so more is understood about potential underlying mechanisms. The virus exists as either non-cytopathogenic (ncp) or cytopathogenic (cp) biotypes, with the ncp biotype causing the majority of field losses. BVDV exhibits vertical transmission from mother to fetusmand can infect the host either transiently or persistently. Acute infection with ncpBVDV in mid gestation increases abortion rates or causes birth of persistently infected (PI) calves. Many of the economic losses attributed to BVDV are, however, due to sub-optimal fertility. Conception rates fall following both experimental and field infections with BVDV around the time of insemination. A recent meta-analysis reported that vaccinated cows not only experienced a reduction in both abortion and fetal infection rates but the risk of becoming pregnant improved by about 5%. A variety of mechanisms have been suggested to account for such effects. Both follicular development and associated steroid production may be impaired leading to oestrous cycle irregularities. BVDV can also colonise the uterus. Mammalian cells normally produce type 1 interferons (IFN) in response to viral infection, which then trigger a cascade of antiviral pathways. BVDV causes immunosuppression through its ability to inhibit IFN production, so delaying the host's responses and enhancing the ability of the virus to complete its replication cycle. This increases susceptibility to bacterial infections and may therefore make infected cows more likely to contract endometritis or mastitis. In cultured bovine endometrial cells we have shown that experimental infection with ncp BVDV inhibited a variety of immune pathways normally activated in response to a challenge with bacterial lipopolysaccharide (LPS), including down-regulation of many interferon stimulated genes (ISGs) which are an important part of uterine defence mechanisms. Infection with ncpBVDV was also able to switch endometrial prostaglandin production from $PGF_{2\alpha}$ to PGE_2 which acts as an immune suppressor.

Maternal recognition of pregnancy in cows is achieved through production of interferon tau (IFNT) by the trophectoderm of the elongating conceptus. IFNT is a type I IFN which acts in concert with progesterone to programme the uterine endometrium to develop a receptive environment for implantation including up-regulation of many ISGs. Acute infection with ncpBVDV interfered with IFNT signalling in the endometrium, suggesting another mechanism whereby infection in early gestation may reduce conception rates by increasing embryo mortality. Turning to BHV-1, this is a major contributing factor to calf pneumonia, which remains the most common cause of mortality and morbidity in dairy calves between one to five months of age. This is often associated with bronchopneumonic lesions and pleural adhesions and can slow growth in pre-pubertal heifers, delay breeding and increase age at first calving. Previously infected animals subsequently show reduced fertility and are more likely to be culled in their first lactation. Both BHV-1 and BHV-4 remain latent in the host following initial infection and may be reactivated later by stress, for example associated with calving and early lactation. Information of direct effects of BHV-1 on the reproductive tract is sparse, but there is some evidence that infection can have a direct effect on ovarian function. While BHV-4 is cytopathic and can readily infect the uterus, this alone may not reduce fertility. It appears instead to act as a co-factor with established bacterial pathogens such as *E. coli* and *A. pyogenes* to promote the development of endometritis and delay uterine repair mechanisms after calving. Infected animals have been reported to require more services to conceive and have delayed conception. Both Schmallenberg virus (SBV) and Bluetongue virus (BTV) are transmitted by insect vectors and lead to increased abortion rates and congenital malformations. SBV first emerged in Europe in 2011. The clinical signs of disease in adult cows are quite mild and include fever, a drop in milk yield and diarrhoea but the virus can both persist in and cross the placenta to replicate in the fetus itself resulting in abortion or severe congenital malformations causing dystocia and birth of non viable calves. Whilst these effects on the fetus are the most obvious sign of disease, there is also evidence for adverse effects on establishment of pregnancy and/or early embryo development. There was a small but demonstrable decline in fertility parameters during the 2011 European epidemic, including a significant increase in the number of repeat inseminations required and a fall of about 5% in the 56 day non return rate. The geographical distribution of BTV-8 is primarily dependent on the distribution of Culicoides midges, which are the insect vectors. Apart from potentially causing high morbidity and mortality and reduced milk production, BTV also affects reproductive performance in dairy cows. The virus can cross the placenta and fetuses infected before 130 days of gestation develop fatal malformations. There is also epidemiological evidence for lower conception rates and longer calving to conception intervals in cattle which have been inseminated from 4 weeks before until 5 weeks after the date of disease detection within the herd. Hatched blastocysts are susceptible to BTV-8 infection, showing growth arrest and increased apoptosis. In summary, although the reductions in conception rates due to viral infections are often hard to quantify, they are nevertheless sufficient to cause economic losses which help to justify the benefits of vaccination and eradication schemes.