Pathophysiology of abortion in cattle.

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Summary

Pathological lesions and inflammatory cell infiltrations in the placenta associated with abortion in cattle do not appear to be so severe or diffuse as to suggest that inflammatory or immunological responses are responsible for the explusion of the fetus. A failure of trophoblast to secrete progesterone and other steroid hormones, as a result of degeneration or necrosis related to infection increases the excitability of the myometrium. Uterine contractions expel the fetus in the absence of the hormonal cascade which normally controls the "fetal ejection reflex".

Introduction

The desirable outcome of any pregnancy is the successful delivery of a live fetus, capable of surviving as a freeliving creature. Anatomical and physiological adaptations in the female allow the product of conception to be nourished and protected within the mother; alterations in maternal endocrine and immune systems allow the fetal allograft to grow in what is potentially a hostile environment. The evolutionary advantage conferred on animals which have developed this method of fetal protection is shown by the predominance of certain species.

The failure rate of pregnancy may be as high as 50% (Hendrickx and Binkherd 1980). Fosgate and Smith (1954) found that 6.4% of bovine fetuses were lost between 34 days and full-term; Murray (1989) has found the abortion rate in dairy cattle to be 2% after 100 days gestation or over. In man, 25% of aborted macerated fetuses and 5% of those that are fresh have chromosomal abnormalities (Warburton and others 1980); hence the opinion that abortion is a necessary safety mechanism which ensures that genetic defects in the population are restricted. A similar explanation for abortion in sheep and cattle has been rejected by Berepubo (1979).

In cattle breeding, premature delivery of a fetus is a disaster; if it is alive, its chances of survival are significantly reduced; if the fetus is dead, the loss is obvious. The dam is usually culled on economic grounds because her milk yield will be significantly reduced, and there is always the fear that she will not quickly become pregnant again. With the current number of abortions reported in the United Kingdom annually at around 30,000, the economic losses associated with abortion in cattle can be estimated at 16 million.

Abortion in sheep and cattle is often associated with infection. From late Victorian times, enzootic abortion (brucellosis) in cattle has been identifed as a disease with both serious financial and public health implications. With its eradication in the late 1970's farmers thought that abortion would be a "thing of the past". This has not happened. The fact that toxoplasma and chlamydial infections in sheep are the most common and easily diagnosed causes of abortion has kept infectious abortion very much to the fore in the minds of stockmen and veterinarians alike. It is frustrating to all parties that the current diagnostic rate for abortion investigations in cattle by veterinary laboratories is about 6%.

This paper briefly examines the mechanisms controlling pregnancy and parturition, and describes how pathological changes found in aborted placenta and fetus can be used to elucidate the physiological changes involved.

Mechanisms controlling parturition in cattle.

Pregnancy in cattle and sheep is terminated through hormonal changes, which originate from the fetal pituitary, initiating a "fetus ejection reflex". As the fetus matures, its adrenal gland becomes more responsive to adrenocorticotrophic hormone (ACTH), so that fetal blood cortisol concentrations rise during the last third of pregnancy (Bassett and Thorburn 1973). This, in turn, is a stimulus to the cholesterol metabolic pathway in the placenta; the progesterone end-point of steroidogenesis becomes extended towards production of oestrogens-mostly oestradiol-17 and oestrone-as shown in Figure 1 (Hunter and others 1977). By this mechanism the birth canal and mammary gland are prepared for parturition. Synthesis of prostaglandins is triggered by placental oestrogens.

This process in cattle can be mimicked using exogenous corticosteroids and/or prostaglandin to bring about abortion in cattle from 150 days onwards (Kaker, Murray and Dobson 1984).

The placentome has been identified as the site of synthesis of oestrone sulphate (Mattiolo and others 1984) and placental prostaglandin (Gross and Williams 1988) in pregnant cattle. Progesterone synthesis may be sited within fetal trophoblast cells, diffusing across the basement mem-

Figure 1. Concentrations of oestrone sulphate, oestradiol sulphate in allantoic and amniotic fluid during stages of pregnancy in the cow.

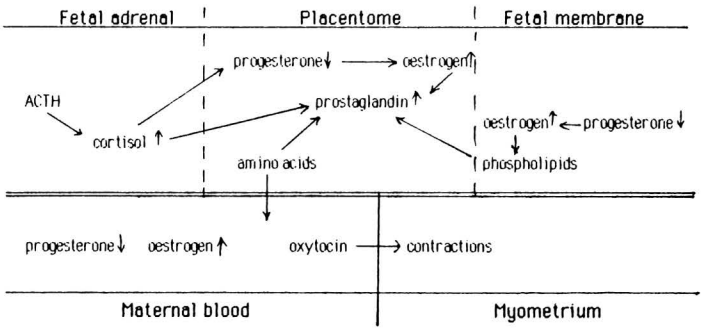
oestrogen sulpates ng/ml

Day of gestation	oestrone		oestradiol 17		oestradiol 17	
	A	B	A	B	A	B
132	465	200	30.0	15.0	5.4	0.8
162	60	15	3.9	60.0	2.6	0.9
192	190	25	8.9	30.0	0.5	0.3
250	80	10	12.0	15.0	7.8	0.5

A: allantoic fluid B: amninotic fluid

branes and cell junctions into the maternal blood circulation, where it directly suppresses myometrial prostaglandin secretion and oxytocin receptors. Trophoblast cells may also react to immunohistological staining for oestradiol-17 very near to full term in cattle, steroidogenesis being under the control of the -hydroxylase enzyme system which is activated by fetal cortisol. The interrelationships are represented in Figure 2.

Figure 2. Schematic representation of physiological influences affecting parturition.



Immunological failure as a cause of abortion.

Abortion may occur through failure of several adaptive strategies which normally maintain pregnancy, and failure of the dam's immunological system to tolerate the fetal allograft is one of them. There is an argument that any inflammatory process at the feto-maternal interface in the placentome will provoke abortion via immunological rejection. This idea presumes that expression of "foreign" fetal antigen on trophoblast cells can be clearly recognized, as a result of degeneration or necrosis of these cells, and a substantial inflammatory response should indicate that rejection has occurred.

A study of aborted placental material taken from over 150 abortion investigations does not entirely support this hypothesis. There are three general patterns of histopathological change:

a) diffuse tissue degeneration accompanied by mild inflammatory cell infiltration, with or without oedema (Figure 3).
b) multiple focal inflammatory lesions, with moderate/severe polymorphonuclear or mononuclear cell infiltration and tissue cell necrosis (Figure 4).
c) vascular lesions, characterized by haemorrhage or oedema (Figure 5).

Figure 3. Diffuse trophoblast cell degeneration→ ; pyknosis, swelling, and cell lysis are widespread. Some mineralisation is evident ⇨. A mild inflammatory cell infiltration is present in maternal septae (m). x 212.

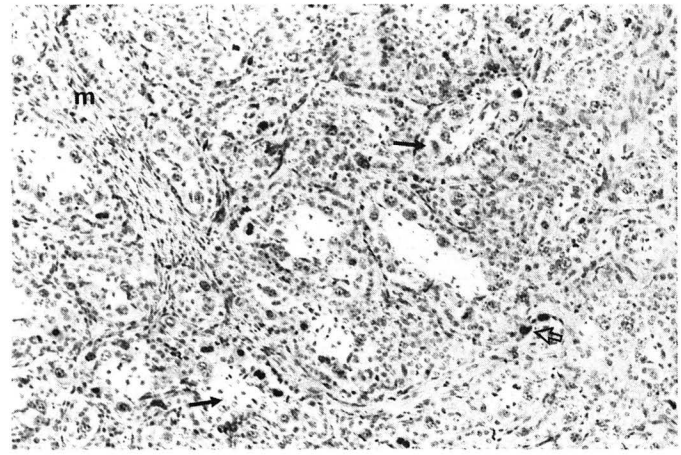


Figure 4. Multiple focal inflammatory lesions in chorio-allantoic villi. Widespread polymorphonuclear inflammatory cell infiltration; aggregations of cells surround areas of villus necrosis. Some congestion is present in villus capillaries. x 212.

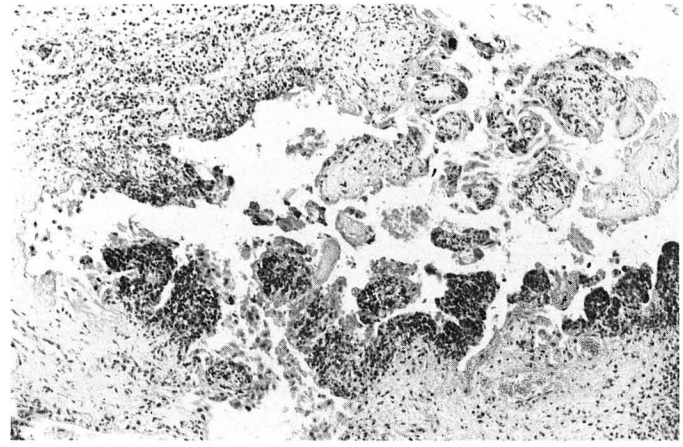
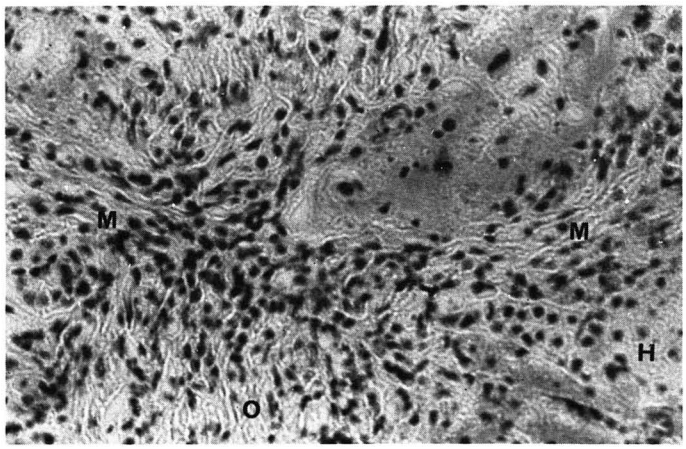


Figure 5. Widespread vasculitis with substantial mixed inflammatory cell infiltration in maternal septae (M). Oedema is present (o) with some haemorrhage in chorioallantoic vill (H). x 540.



By far the most common finding is widespread degenerative change in the placenta. This observation has led a number of workers in this field to regard placental histology as being worthless in abortion investigations, since these changes are similar to those found in the uterus and fetal membranes of normal post-partum cows (Jerrett and McOrist 1985). If this opinion is true, then the expected inflammatory cell response which ought to accompany an immune rejection response is absent, and suggests that this mechanism does not play a significant role in initiating abortion in cattle.

In a number of abortions associated with Bovine Viral Diarrhoea virus (BVD), extensive mineralisation of trophoblast is accompanied by some inflammatory cell infiltration and oedema; this may support the idea that degenerative changes can take place over a relatively long period of time. From an immunological standpoint, if trophoblast is somehow protected from maternal antibody, such degenerate cells ought to stimulate a maternal inflammatory response long before they become mineralized.

In sheep, clinical observation supports this view of the role of inflammation in stimulating immune rejection. Preabortion treatment of pregnant ewes with antibiotics in the face of known chlamydia infection can reduce the abortion rate by about one-half (Greig, Linklater, and Dyson 1982), even though all infected ewes shed infective chlamydia whether they had aborted or delivered full-term fetuses. The precise explanation of this observation is not known, although it must depend on the degree of placental damage incurred from the infection.

Inflammatory infiltration and trophoblast degeneration in the decidua and basal plate of human placenta are present in 85% of normal pregnancies (Schneider 1970). These changes do not compromise the pregnancy. Villitis is an important pathological finding in the human placenta; the vast majority are of unknown origin. It has been suggested that a graft-versus-host reaction is involved in the aetiology of this lesion rather than vice-versa (Knox and Fox 1984).

In this study, 9 cases were identified with this pathology but no cause for the abortion was confirmed.

Multifocal inflammatory and necrotic lesions found in aborted placentae have frequently been associated with bacterial infections, in both bovine (Murray 1989) and human pregnancies (Fox 1978). The lesions are characterized by moderate to severe polymorphonuclear cell infiltrations, with some mononuclear cell involvement. The significance of the lesion in physiological terms may be;

i) that certain bacteria infecting the placenta may stimulate local prostaglandin synthesis by the production of endotoxins which diffuse into the maternal circulation, initiating luteolysis and causing abortion. The endotoxin from *Salmonella typhimurium* can cause luteolysis in the cow (Fredriksson 1984), and potential pathogens such as *E. coli,* Lancefield group B haemolytic streptococci, and *Bacteroides fragilis* increase arachidonic acid metabolism when added to amniotic cell preparations in vitro (Bennett and others 1987).

ii) that prostaglandins of the E and I series are produced by and released from macrophages (Gemsa 1981) as part of the normal inflammatory response.

Perhaps it is this combined effect of the inflammatory process on hormone synthesis and action that Fredriksson and others (1985) alluded to when they described the infectious process of endometritis (toxins, tissue destruction, etc) as stimulating prostaglandin synthesis and release.

The physiological importance of inflammation in the placenta should not be overlooked since degeneration and necrosis of trophoblast may, at the same time, remove the placental source of progesterone and be the stimulus for synthesis of a luteolytic hormone; the net effect will be to increase the excitability of the myometrium, thus triggering off the abortion process.

Vascular lesion in the placenta are associated with *Leptospira hardjo* and Infectious Bovine Rhinotracheitis (I.B.R.) virus infections. The severe pathological lesions in the placenta, and acute septicaemia followed by rapid fetal death which is the sequel to I.B.R. infection ensure that the fetus is aborted 4-7 days after its death (Kendrick 1973). The fetus has no chance of responding to this infection with either an immunological response or a "stress response" from the adrenal gland, since death quickly follows infection. The extent of vascular damage is widespread; it follows that nourishment of the fetus and gaseous diffusion is interfered with. In some abortions associated with *L. hardjo,* where time from fetal infection to death is somewhat longer, there is a discernible increase in haematopoiesis in the liver; this is a response which takes several days and could be related to progressive fetal hypoxia following decreased placental capillary permeabil-

ity, associated with vascular damage. Again, the abortion process seems to be independent of the degree of actual pathological change in the placenta.

Failure of physiological adaptation in pregnancy.

Endocrinology.

Failure of the corpus luteum of pregnancy during the first 150 day gestation causes abortion in cattle so that prostaglandin treatment at this stage of pregnancy induces abortion.

Death of the young fetus (Crown-rump length 20cm to 35cm) does not necessarily cause luteolysis with fetal expulsion; such a fetus frequently remains in utero, undergoing autolysis, dehydration, and mummification over a period of many weeks before abortion occurs. Fetal membranes remain remarkably intact during the process, so that cotyledonary gross structure may still be discernible. The precise mechanism which allows this process to take place is unknown.

Damage to the trophoblast -either from infection or other causes, leading to degeneration or necrosis-will lead to a reduction in its synthetic function (Chard and Klopper 1982). Blood concentration of progesterone in aborting cattle and sheep should be demonstrably lower than in normal pregnancy but this is not so; it is more likely to reflect ovarian function than placental production. However, it may be assumed that placental progesterone secretion is reduced in these circumstances.

Bacterial, fungal, or viral infection of placental membranes, followed by trophoblast degeneration and/or necrosis should reduce the placental synthesis of progesterone, although the luteal source will remain. However, if the products of inflammation stimulate prostaglandin synthesis then even this site of progesterone production may be removed; this will increase the contractility and tone of uterine muscle. It is known that the contractility of the myometrium to prostaglandin increases in the absence of progesterone during early human pregnancy (Swahn and others 1989).

Oestrogens play an important role in preparing the pregnant cow for parturition. Should the fetus die as a result of infection and trophoblast cells degenerate, then neither the fetus nor placenta can supply oestrogens prior to abortion. There are naturally high concentrations of this hormone in chorio-allantoic and amniotic fluids, but fetal vascular stasis following death will prevent oestrogens diffusing efficiently through the feto-maternal barrier to influence the birth process. With abortion of a live fetus the hormonal cascade may operate normally, since the fetal pituitary-adrenal axis remains functional.

There is much clinical evidence to support the hypothesis that the normal fetus ejection reflex does not operate in some abortions. Stockmen commonly remark that they have no idea that a pregnant cow is going to abort, because there is lack of udder development, little slackening of pelvic ligaments, and absence of vulval softening. Particularly in the udders of aborting heifers, there is little milk to be found; a sticky, thick secretion indicates that the initiation of lactogenesis has not taken place. The veterinary obstetrician knows that the delivery of a seven month aborted fetus can be difficult. Some of the worst calvings that we are asked to undertake are those associated with *S. dublin* and *Corynebacterium pyogenes* abortions at 220 to 240 days gestation; not only are placental fluids absent and the fetus autolysed, but the lack of genital tract dilation and relaxation reduces the space in the tract through which the fetus can be dragged; the uterus is also contracted hard around the dead fetus.

Myometrial contractility.

The onset of myometrial contractions is not associated with increased maternal blood oxytocin concentration, and it is unlikely that this hormone plays any essential role in the initiation of labour. Spontaneous contractions occur throughout pregnancy (Fuchs 1978). Progesterone concentrations present during pregnancy ensure that the required threshold dose of oxytocin is too high to initiate myometrial contractions. The steroid hormones modulate the quality of the receptor molecules in the myomentrium and the numbers of oxytocin and oestrogen receptors rise near full term (Soloff 1977). However, the uterus is not always "quiescent" during pregnancy. Fuchs (1978) described the uterus of pregnant rats as spontaneously contracting throughout pregnancy and not being refractory to oxytocin at any stage. But progesterone has a suppressive action on uterine contractility, and its removal may produce fetal hypoxia through:

a) direct fetal circulatory embarrassment as a result of increased uterine activity.
b) placental separation at the caruncle, reducing exchange of nutrients and gases between dam and fetus.

However, the role of progesterone in the maintenance of pregnancy is rather equivocal. In human obstetrics, administration of exogenous progesterone cannot halt threatened abortion (Rudel, Kincl, and Henzl 1973) and the same is probably true in mares.

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