

A New Approach to Repeat Breeding in Cows: Treatments Targeting the Endometrial Growth Factor-cytokine Network

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Abstract

Repeat breeder (RB) cows have been reported to have an alteration in ovarian steroid concentrations in the circulation. The endocrine alteration disturbs the endometrial growth factor-cytokine network in the endometrium and, in turn, may cause embryonic death in RB cows. An example may be loss of peaks in the cyclic change of epidermal growth factor (EGF) concentrations in the endometrium. This alteration of the EGF profile can be found in 70% of RB cows in high yielding dairy herds. Hormonal treatment with a high dose of oestradiol and infusion of seminal plasma normalizes the endometrial EGF profile and restored fertility. The treatments targeting the endometrial regulatory network may become an effective option to deal with RB cows.

Keywords: cow, endometrium, epidermal growth factor, repeat breeder

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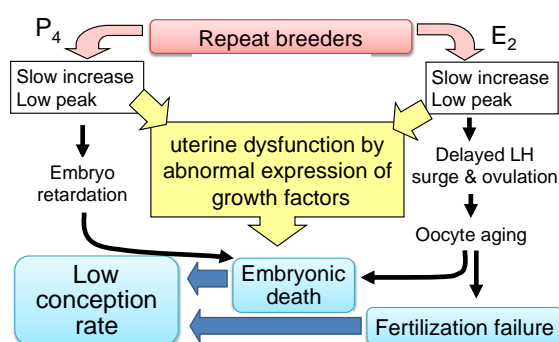


Figure 1. Endocrine disorders and potential mechanism impairing fertility in repeat breeders

Endocrine disorders in RB cows

An important source of economic loss in dairy herds is the presence of RB cows that fail to conceive after three or more inseminations without detectable abnormalities in their genital tracts and with apparently normal estrus cycles. Causes of infertility in RB cows are usually unclear, but probably include management, environmental and animal factors (Peters, 1996; Levine, 1999). In RB cows, early embryonic loss caused by improper uterine environment is linked to endocrine disorders that include ovarian steroid hormone concentrations (Fig 1). However, endocrine disorders in RBs are inconsistent between reports and lack firm evidence (Levine, 1999). Thus, a marker of altered endocrine environment that is more sensitive and accurate than steroid hormone concentrations is needed to diagnose RB cows with endocrine abnormalities.

Alteration of the endometrial EGF profile in RB cows

We reported the presence of RB cows that exhibit abnormality in the growth factor-cytokine network. A loss of the cyclic change in endometrial EGF concentrations during the oestrous cycle represents the abnormality of the regulatory network. Cyclic cows have two peaks of EGF concentrations; on days 2-4 and 13-14 of the oestrous cycle (Fig 2) (Katagiri and Takahashi, 2004). The peaks of endometrial EGF concentrations, however, have lost or lowered in RB cows. This alteration was found in about 70% of RB cows and lasted at least 3 consecutive oestrous cycles.

Potential relationship between the EGF profile and fertility

Production of EGF in the uterine endometrium is regulated by ovarian steroid hormones; namely oestradiol and progesterone. Thus, alterations in the endometrial EGF concentrations in RB cows may reflect an impaired endocrine environment that may cause early embryonic loss. The potential roles of EGF in embryonic development and uterine function may suggest that the loss of the cyclic change in the endometrial EGF concentrations connected endocrine disorders and increased embryonic mortality in RB

cows. In a preliminary study (Katagiri and Takahashi, 2006), RB cows with an altered endometrial EGF profile were treated, again examined for the EGF

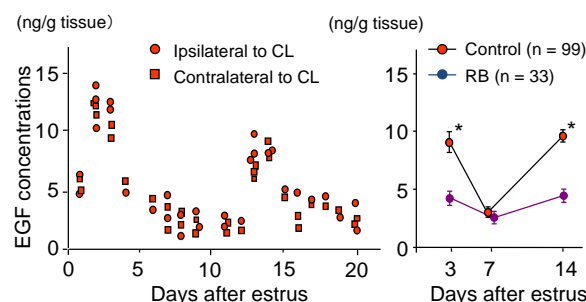


Figure 2. EGF concentrations in the bovine endometrial tissues in normal and RB cows

profile. The cows were then inseminated during the next two oestrous cycles. Cows with a normalized EGF profile (78.6%, n=14) after treatment had a greater pregnancy rate than those with an altered profile (25.0%, n=12) (Katagiri and Takahashi, 2006). Furthermore, embryo transfer recipients with low EGF concentrations on Day 3 showed lower conception rate (76.9%, n=350) than those with the normal levels of EGF concentrations (33.3%, n=87) (Katagiri, 2006). Thus, potential relationship between the altered endometrial EGF profile and fertility seems evident in RB cows, and even in the apparently normal population.

Treatment with a high-dose of estradiol or seminal plasma targeting an altered EGF profile in RB cows

We have developed hormonal treatment and been developing a new treatment with seminal protein targeting endometrial EGF production. RB cows with an altered EGF profile were treated with a CIDR program in combination with a high dose (5 mg) of oestradiol benzoate. The treatment normalized the endometrial EGF profile in 67% of cows and increased pregnancy rate after 2 inseminations than those with altered profiles (67 vs. 17%) (Katagiri and Takahashi, 2008). The results confirmed potential relationship between normalization of the endometrial EGF profile and restoration of fertility.

Seminal plasma contains proteins regulating function of the sperm and female genital tracts in different species. In RB cows, seminal plasma infused into the vagina, but not uterus, increased endometrial EGF concentrations on days 3 and 14. The normalization of EGF peaks resulted in restoration of fertility. Seminal plasma was, then, separated by gel filtration and electrophoresis and tested an activity to increase EGF concentrations in the endometrium. The study revealed that protein(s) with MW of 16-29 kDa and pI 5.8-7.0 had the activity. Further study to identify protein that is responsible for this activity is being undertaken. In addition, mechanisms, by which seminal protein infused into the vagina affects endometrial EGF levels, need to be studied to develop an effective treatment targeting the endometrial growth factor-cytokine network.

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