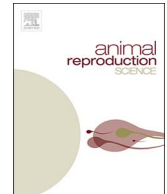




Contents lists available at ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

Effects of oxytocin and PGF_{2α} on uterine contractility in cows with and without metritis—An *in-vitro* study

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ARTICLE INFO

Keywords:

Uterus
Puerperium
Sonomicrometry
Extracorporeal perfusion

ABSTRACT

The aim of this study was to investigate the effects of PGF_{2α} and oxytocin *in vitro* on myometrial contractility in puerperal uteri. Thirteen puerperal uteri were removed and perfused after euthanasia of cows with ($n = 7$) and without metritis ($n = 6$). Measurement of uterine contractility was done using four piezoelectric crystals, which were implanted into the myometrium along the greater curvature of the uterine horn where fetal implantation occurred during the previous pregnancy. After 30 min of equilibration, oxytocin (5 IU) or PGF_{2α} (2.5 mg Dinoprost) was administered randomly into both uterine arteries, and 30 min later, the second administration of either oxytocin or PGF_{2α} occurred. Treatment with oxytocin induced contractions in uteri with metritis and uteri without metritis ($P < 0.05$). In uteri with metritis, greater uterine contractions occurred after stimulation with oxytocin than in uteri without metritis ($P < 0.05$). Treatment with PGF_{2α} did not ($P > 0.05$) result in increased contractions in the uteri without metritis, however, induced an initial decrease in contractions followed by an increase ($P < 0.05$) in contractions in uteri with metritis. Myometrial and endometrial gene expression of PGF_{2α} (FPR) and oxytocin receptor (OTR) was greater ($P < 0.05$) in uteri with metritis than in uteri without metritis. The results suggest that oxytocin, but not PGF_{2α}, is an effective uterotonic drug in puerperal cows. Uteri in which metritis was diagnosed contracted more strongly after treatment with oxytocin than uteri in which metritis was not diagnosed. This effect was paralleled by greater gene expression of OTR as well as FPR in uteri with metritis compared with uteri in which metritis was not diagnosed.

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<https://doi.org/10.1016/j.anireprosci.2017.11.019>

Received 18 August 2017; Received in revised form 7 November 2017; Accepted 22 November 2017

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1. Introduction

Puerperal uterine diseases, including retained fetal membranes and metritis, are important in dairy cows (Esslemont and Peeler, 1993; Drillich et al., 2001;) for various reasons. Substantial economic loss stems from decreased milk yield, reduced fertility, increased treatment costs, and greater culling rates (Bartlett et al., 1986; Esslemont and Peeler, 1993; Lewis, 1997). Metritis is characterized by uterine enlargement and fetid lochia with or without systemic illness. Metritis usually occurs in the first 10 days after parturition and is associated with delayed uterine involution (Sheldon et al., 2006).

In addition to local and systemic antibiotics (Smith et al., 1998; Drillich et al., 2001), treatment of puerperal uterine diseases often includes uterotonic agents such as PGF_{2α} and oxytocin. Theoretically, these drugs could be expected to increase uterine contractility thereby promoting drainage of uterine contents and enhancing uterine involution and, eventually, fertility (Bajcsy et al., 2006). Reports on the effects of uterotonic agents on uterine contractility and subsequent fertility are ambiguous (Frazer, 2005). Oxytocin has consistently been reported to have a positive effect on uterine contractility (Eiler et al., 1984; Kündig et al., 1990a; Gajewski et al., 1999; Bajcsy et al., 2006), but its use in the early puerperal period had no effect on reproductive performance in healthy cows and cows with uterine diseases (Tian and Noakes, 1991; Barrett et al., 2009; Jeremejeva et al., 2010). Prostaglandin F_{2α} treatment of healthy postpartum cows had positive (Kündig et al., 1990a; Gajewski et al., 1999) or no effects (Eiler et al., 1981; Kündig et al., 1990a) on myometrial contractility. Fertility of dairy cows was positively affected (Young et al., 1984; Nakao et al., 1997; Melendez et al., 2004) or not affected (Tian and Noakes, 1991; Jeremejeva et al., 2010; Jeremejeva et al., 2012) by PGF_{2α} treatment in the early postpartum period. Of note, the cited studies did not include cows with puerperal uterine disease when assessing the effect of uterotonics on uterine contractility.

In addition to oxytocin and PGF_{2α}, other hormones are involved in uterine contractility in cows. Estrogen and progesterone (P4) have indirect as well as direct effects on myometrial contractility (Hixon and Flint, 1987; Fomin et al., 1999). For a hormone to have an effect on a target cell, it must first bind to its receptor. The efficacy of a hormone, therefore, depends not only on the concentration of the hormone but also on the numbers of receptors in the target organ. To our knowledge, uterine expression of receptor genes of ecbolic hormones has not been previously investigated in cows in the early puerperal period.

Uterine contractility can be investigated *in vitro* using isolated perfused uteri or myometrial strips mounted in an organ bath (Hirsbrunner et al., 2002; Gorriz-Martin et al., 2017). Compared with other *in-vitro* techniques, extracorporeal perfusion of organs allows estimation of the electric and mechanic activity of the whole organ and preserves the structure and function of the organ (Dittrich et al., 2003). Several studies reported that the model of isolated perfused uteri is suitable for measuring uterine contractility as well as investigating the effects of uterotonics and tocolytics in humans (Bulletti et al., 2004; Richter et al., 2006), swine (Dittrich et al., 2003; Künzel et al., 2014), and cattle (Bock, 2004). Comparison of the effects of oxytocin on uterine contractility obtained using extracorporeally perfused uteri and an *in-vivo* model in cattle showed basic agreement between the two methods (Bock, 2004).

Sonomicrometry is a novel technique which has been used successfully for *in-vivo* assessment of uterine involution (Heppelmann et al., 2015a; Heppelmann et al., 2015b) and for measuring the cervical diameter in the periparturient period in dairy cows (Breeveld-Dwarkasin et al., 2002; Van Engelen et al., 2007). Sonomicrometry allows the objective measurement of the distance between individual piezoelectric crystals based on the time an ultrasonic signal requires to travel between a transmitter and a receiver (Adelson and Million, 2004). This technique has also been used for investigation of cardiac and skeletal muscle contractility in different species (Horiuchi et al., 2012; Robertson and Biewener, 2012; Askov et al., 2013).

The primary goal of this study was to investigate the effects of PGF_{2α} and oxytocin on myometrial contractility using sonomicrometry in isolated perfused uteri from euthanized puerperal cows with and without metritis. In the present study, it was hypothesized that PGF_{2α} and oxytocin would have no effect on uterine contractility in the early puerperal period, particularly in uterine specimens collected from cows with metritis. It was speculated that findings associated with acceptance of this hypothesis would contribute to a reduction in the use of hormones in dairy cows. A secondary goal was to examine the gene expression for hormonal receptors (estrogen receptor α [ER α], progesterone receptor [PR], PGF_{2α} receptor [FPR], and oxytocin receptor [OTR]) in these uteri.

2. Materials and methods

2.1. Uteri

The uteri were taken from 13 Holstein Friesian cows that were euthanized 5–21 days postpartum. Reasons for euthanasia were traumatic diseases of the locomotor system ($n = 3$), lameness ($n = 2$), peritonitis ($n = 2$), endocarditis ($n = 1$), pericarditis ($n = 1$), amyloid nephrosis ($n = 1$), bronchopneumonia ($n = 1$), sepsis ($n = 1$), and posterior functional stenosis ($n = 1$). All cows were patients of the Clinic for Cattle of the University of Veterinary Medicine, Hannover, Germany.

2.2. Study design

Blood samples were collected from a jugular vein into EDTA and serum tubes (Sarstedt AG & Co, Nürnberg, Germany) for hormone analysis. The cows were euthanized by intravenous injection of 30 g of pentobarbital sodium (Release[®], WDT eG, Garbsen, Germany). A transverse incision was then made in the ventral abdomen of the dead cows and the uterus including the cervix and ovaries was immediately removed. The uterine blood vessels were immediately flushed with heparinized (Heparin-Natrium Braun, B. Braun Melsungen AG, Melsungen, Germany; 150 IU/mL medium) Tyrodés solution containing 136.8 mmol/L NaCl, 5.5 mmol/L glucose*H₂O, 11.9 mmol/L NaHCO₃, 2.7 mmol/L KCl, 0.416 mmol/L NaH₂PO₄, 1.05 mmol/L MgCl₂*6H₂O, and 1.8 mmol/L

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