Original article

Clinical observations on the course of oxytocin- or prostaglandin E2/oxytocin-induced parturition in mares

M. Witkowski[1], K. Pawłowski[2]

[1] Department of Animal Reproduction and Anatomy, University of Agriculture in Cracow,
Al. Mickiewicza 24/28, 30-159, Cracow, Poland
[2] Faculty of Veterinary Medicine, University of Life Sciences, SGGW,
Nowoursynowska 159c, 02-787 Warsaw, Poland

Abstract

The objective of this study was to compare the course of parturitions induced with sole oxytocin with those induced with the combination of intracervical prostaglandin E2 jelly and oxytocin. For this purpose 13 mares in advanced pregnancy were allocated to the groups pretreated with either intracervical PGE2 (experimental group) or saline (control group) two hours before intravenous oxytocin (5 IU) administration. The mares were compared with respect to cervical dilation diameter (CDD) 20 min. after oxytocin injection. Time intervals from the first oxytocin dose to: the first external signs of parturition, the chorioallantois rupture, the delivery of a foal and time interval from the delivery of a foal to the placenta separation were measured.

Cervical dilatation diameter as well as proportion of mares with cervical dilatation > 20 cm were significantly higher in the group of PGE2 treated mares comparing with control group (p = 0.0115 and p = 0.0490, respectively). All time intervals measured were statistically insignificant for both groups of mares, however time intervals from the first oxytocin dose to the first external signs of parturition, to the allantochorion rupture and to the delivery of a foal, were very close to the significance level (α = 0.05).

To conclude, PGE/oxytocin combination has positive influence on the preparation of the uterine cervix to parturition. Moreover, it seems that PGE2 pretreatment reduced total oxytocin dose for successful parturition induction and shortened time elapsing between the first oxytocin dose and the delivery of a foal what is crucial for foal's safety.

Key words: parturition induction, mare, PGE2, oxytocin

Introduction

The endocrine regulation of equine parturition involves progestagens, oestrogens, prostaglandins and oxytocin as in other species but in many aspects is an unique one. Total progestagen concentrations rise and total oestrogen levels fall in the mare during the last 20-30 days of gestation and show changes typical

Correspondence to: M. Witkowski, e-mail: mawitkow@gmail.com, tel./fax: +48 12 662 41 13

of impending parturition in other species only in the last 24-48 h before delivery. Fetal cortisol concentrations also rise late in gestation in the horse compared to other species. In common with other species, the prepartum endocrine cascade appears to begin in the fetal horse with activation of the fetal HPA axis. Close to term in association with increasing fetal ACTH levels, the fetal equine adrenals appear to switch to producing cortisol which induces a rapid fetal maturation and may also contribute to increased uteroplacental oestradiol-17 beta and prostaglandine production. Finally, increased prostaglandine secretion activates myometrial contractions, which stimulate oxytocin release via a neuroendocrine reflex (Fowden et al. 2008).

Delivery in a mare can be induced with oxytocin (Hillman 1975, Macpherson et al. 1977, Purvis 1977, Meyers and Le Blanc 1991, Witkowski 2007), PGF2α (Jeffcott and Rossdale 1977, Ley et al. 1994) and glicocorticosteroids (Alm et al. 1974, 1975). None of those methods is perfect, however, most authors agree, that a medicine of choice is oxytocin due to immediate and predictable effect (Jeffcott and Rossdale 1977, Bennett 1988). In some cases combinations of oxytocin and other agents are recommended. To hasten fetus maturation, corticosteroids are indicated before oxytocin treatment (Alm et al. 1974, 1975, First and Allen 1977), in cases of insufficient uterine cervix relaxation, PGE pretreatment should be considered (Rigby et al. 1998). As shown, variety of agents and protocols have been used successfully to induce parturition in mares and this procedure is useful in a wide range of medical and management situations. Even though undoubtedly useful, induction of parturition remains a brutal interference in the physiological process and poses risk of side effects, like premature placental separation, dystocia, fetal dysmaturity and fetal hypoxia (Alm at al. 1975, Jeffcott and Rossdale 1977). Because of this facts a method for induction of the parturition which would closely mimic the natural parturition, still remains a challenge.

The objective of this study was to compare the course of parturitions induced with sole oxytocin with those induced with the combination of intracervical prostaglandin E2 jelly and small doses of intravenous oxytocin.

Materials and Methods

The induction of the parturition was carried out on 13 healthy, multiparous mares of different races (1 thorouhbred, 2 arabians, 10 warmblood), aged 5-10 years, with minimal pregnancy duration of 345 days.

Mares were assigned to one of the two experimental groups with respect to obtain approximately equal groups considering their type and pregnancy duration (349 ± 5.7 and 348 ± 3.6 days for experimental and control group, respectively). Parturitions were induced on account of either customer's request or severe lactation only if mammary secretion calcium concentration (measured with flame spectrophotometer) was >10 mmol/L indicating fetal maturity (Ousey at al. 1984, Le Blanc 1988, Ley at el. 1993).

Prior to induction, each mare was examined *per rectum* and *per vaginam* to determine fetus presentation and softness as well as potential dilation of the uterine cervix. Clinical examination performed before saline or PGE treatment revealed that fetuses were in anterior presentation and the uterine cervices were closed. Immediately after examination in 6 mares (experimental group) 1 mg (6 ml) of PGE2 in a jelly form (dinoprostonum, Prepidil®, Pfizer) was inserted 20 mm inside the uterine cervix lumen using deep intrauterine insemination pipette with inner catheter (Minitube of America). As pericervical manipulations may trigger parturition in pregnant mares 7 remaining mares (control group) underwent the same procedure with 6 ml of 0.9% saline introduced into the uterine cervix as a placebo. All mares were observed during the following period and underwent rectal and vaginal examination 2 hours after PGE or saline insertion in order to evaluate changes of cervical tonus and dilation. In mares from both groups short-term discomfort manifested through tail raising and pacing began immediately after pericervical manipulation and disappeared within 10 min. Moreover, in mares from the experimental group unease with signs of a slight abdominal discomfort (urinating position, tail raising) occurred within 30 min. of the medicine deposition and waned gradually during the next hour. Subsequently 5 IU of oxytocin (Inj. Oxytocini, Biowet Puławy) were given to each mare via intravenous catheter placed in the jugular vein and their behavior was monitored for the noticeable straining being the first external sign of parturition. Twenty minutes later each mare underwent vaginal examination and cervical dilation diameter (CDD) was estimated on the basis of manual examination of the cervix. If CDD <20 cm or no external parturition signs present, an additional dose of oxytocin (10 IU i.v.) was given to hasten parturition. In these cases follow-up examinations were performed every 10 min., with principle that if necessary, next oxytocin boluses of 10 IU would be administered to reach an expected stage of parturition.

One of the major presumptions of this study was that interval between the first signs of parturition and the delivery of a foal should not exceed 30 min. (Van-

deplassche 1980). Newborn foals were clinically examined in the first and fourth minute post partum and evaluated according to the 8-point neonatal foal distress score (Martens 1982).

Four time intervals characterizing the course of induced parturition [from the first oxytocin dose to: the first external signs of parturition (OTES) / the allantochorion rupture (OTCA) / the delivery of a foal (OTDE) and time interval from the delivery of a foal to the placenta separation (DEPS)] were recorded (Fig. 1) and compared between the experimental and control group using t-Student test for unpaired samples. The same test was used to compare OTCA, OTDE and DEPS between mares with CDD <20cm and >20cm. Proportion of mares with CDD >20 cm in the experimental and control group was analyzed with Fisher exact test. Significance level (α) was 0.05 in all analyses. Numerical variables were presented as the arithmetic mean (standard deviation). Statistical analyses were carried out in Statistica 10.0.0 (Statsoft) and diagrams were prepared in Microsoft Office Excel 2007 (Microsoft).

Results

In all 13 mares foals were delivered within 30 min. of the first signs of parturition (range 14-30 min., arithmetic mean of 22 min.). Both cervical dilation diameter 20 min. after the first oxytocine dose (CDD) and proportion of mares with CDD >20 cm were significantly higher in the PGE2 treated group (Fig. 1, 2). Differences between time intervals: from the first oxytocine dose to the external signs of parturition (OTES), from the first oxytocin dose to the rupture of allantochorion (OTCA) and from the first oxytocin dose to the delivery of the foal (OTDE) for both groups of mares were statistically insignificant however, very close to the significance level (Table 1). Furthermore, both OTCA and OTDE were statistically significantly shorter in mares with CDD >20cm (Table 2). In PGE2 treated group only one mare required an additional dose of oxytocin (10 I.U.) to hasten parturition. In the control group in 5 mares additional doses of oxytocin (single additional dose of oxytocin in 4 mares and 2 doses in 1 mare) were used to complete deliveries in proper time. In one mare from PGE2 treated group and one mare from the control group premature placental separation occurred. In both cases manual rupture of allantochorion was carried out. In this mares, one hour after delivery, manual separation of placenta was performed as well. All other control mares expelled placentas spontaneously and no differences were observed between groups on this field. There

was no difference in the neonatal foal distress score between the experimental and control group (median of 8 in both groups).

Table 1. Mean (±SD) time intervals characterizing the course of induced parturition in the groups.

Parametr	Experimental group (n = 6)	Control group (n = 7)	P
CDD [cm]	27.5 (5.2)	16.7 (7.2)	0.0115*
OTES [min]	15 (4)	23 (11)	0.1078
OTCA [min]	27 (7)	38 (12)	0.0655
OTDE [min]	36 (6)	46 (13)	0.1315
DEPS [min]	72 (42)	84 (43)	0.6193

* statistically significant at $\alpha = 0.05$

Table 2. Mean (±SD) time intervals characterizing the course of induced parturition with respect to the cervix dilation diameter 20 min. after oxytocin administration.

Time interva	Mares with CDD >20 cm (n = 9)	Mares with CDD <20 cm (n = 4)	p
OTCA [min]	28.1 (8.0)	43.8 (11.5)	0.0151*
OTDE [min]	37.4 (6.9)	51.3 (14.5)	0.0345*
DEPS [min]	61.0 (35.0)	111.6 (50.1)	0.0556

* statistically significant at $\alpha = 0.05$

Discussion

In our study, pretreatment with PGE2 seems to influence positively uterine cervix reaction on oxytocin and indirectly reduce the total oxytocin dose required to induce parturition and the length of the second stage of parturition. This effect could be observed despite lower doses of PGE2 and shorter interval between PGE2 insertion and oxytocin treatment than in the other studies (Volkmann et al. 1995, Rigby et al. 1998). Statistically insignificant OTES, OTCA and OTDE might be partly attributed to the low power of statistical analysis which resulted from small group size as well as to the protocol applied in which additional oxytocin doses were used if only progress in parturition was unsatisfactory.

Physiologically PGE is of fetoplacental origin and is likely more important in promoting cervical ripening and spontaneous rupture of the fetal membranes (Snegovskikh et al. 2006). On this account intracervical PGE2 treatment is widely used in human medicine to induce parturition (Bernstein 1993, Chan et al. 2004). The mechanism of the cervix ripening after
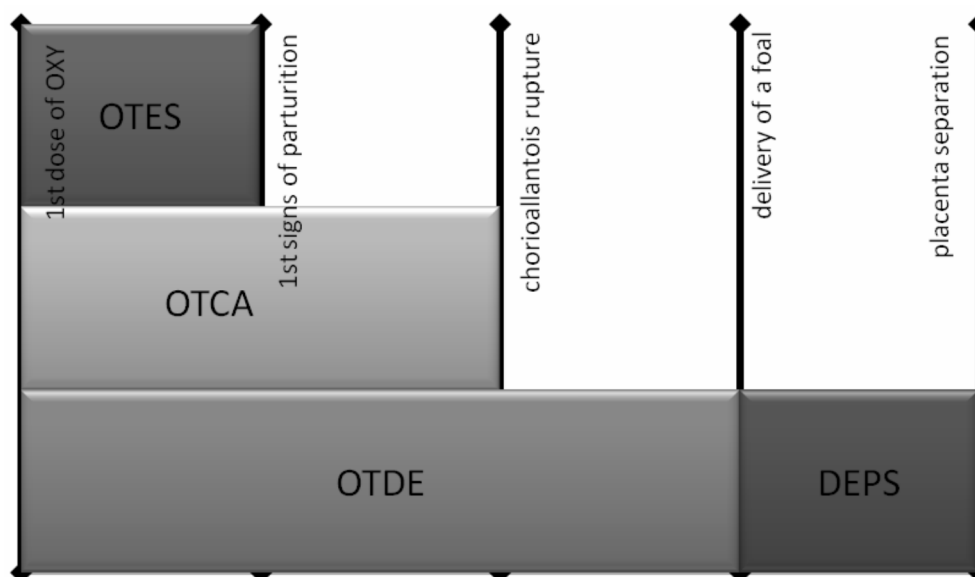
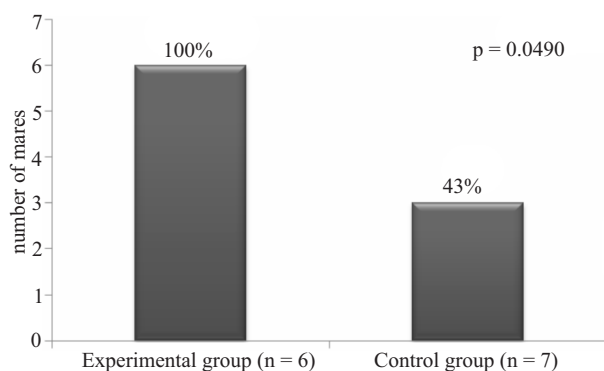Fig. 1. Time intervals characterizing the course of induced parturition.

Fig. 2. Proportion of mares with the cervix dilation diameter >20 cm during examination 20 min. after the first oxytocin dose in the groups.

PGE2 treatment remains unclear but PGE2 is likely to stimulate neutrophils to produce collagenase which in turn disorganizes collagen bundles in the cervix (Kelly 1996, Stjernholm et. al 1999). Some data demonstrate clearly, that cervical ripening is similar to an inflammatory process in which PGE2 stimulatory effect on cytokines plays a crucial role (Dennison et al. 1999, Sennstrom et al. 2000). Intracervical deposition of PGE2 is recommended for women in term with premature rupture of membranes or with low Bishop score and is associated with shorter induction-to-delivery interval, lower rate of cesarean section and decreased maximum oxytocin dose necessary to induce parturition (Ferguson et al. 1988, Chaudchuri et al. 2005).

Thus far two studies have evaluated efficacy and safety of PGE2/oxytocin treatment in inducing parturition in mares. Volkmann et al. (1995) observed reduced foal survival after PGE2 treatment and found this medicine of little value as adjunct to the routine treatment with oxytocin. On the contrary, Rigby et al. (1998) obtained satisfactory results in terms of shortening delivery and promoting foal vigor. In our study no negative influence of PGE2 on newborns condition could be observed. One of the reason of this difference in results when comparing to Volkmann's et al. (1995), could be the fact that we induced parturitions in later pregnancies, what could be crucial for final foal maturation.

As it was mentioned previously, induction of parturition in mares with high doses of oxytocin may result in excessive myometrial activity likely to lead to premature placenta separation or dystocia. On the other hand a small oxytocin dose not only decreases the risk of complications connected with brutal, abrupt delivery but also allows for precise regulation of the delivery course. There are studies in which oxytocin doses even lower than 5 IU were effective in inducing parturitions in mares but in those cases the time of delivery was hardly predictable (Pashen 1980, Camillo at al. 2000). As the second stage of parturition longer than 30 min. carries a risk of fetal hypoxia, protocol based on proposed timing seems to be the most recommended procedure.

To conclude, PGE2/oxytocin combination has positive influence on the uterine cervix preparation to parturition. Moreover, it seems to indirectly reduce the need of additional oxytocin doses and shorten time elapsing between the first oxytocin dose and the delivery of a foal what is in authors' opinion crucial for foal's safety.

It still remains a challenge to select proper dose of PGE and PGE-oxytocin treatment interval, to obtain optimal labor induction.

Acknowledgements

References

Alm CC, Sullivan JJ, First NL (**1974**) Induction of premature parturition by parenteral administration of dexamethoasone in the mare. J Am Vet Med Assoc 165: 721-722.

Alm CC, Sullivan JJ, First NL (**1975**) The effect of corticosteroid (dexamethasone), progesterone, oestrogen and prostaglandine F2α on gestation length in normal and ovariectomized mares. J Reprod Fertil Suppl 23: 637-640.

Bennett DG (**1988**) Artificially controlled versus spontaneous parturition in the mare. Comp Cont Educ Pract Vet 10: 506-516.

Bernstein EP (**1993**) Therapeutic considerations for preinduction cervical ripening withy intracervical prostaglandin E2 gel. J Reprod Med Suppl 38: 73-77.

Camillo F, Marmorini P, Romagnoli S, Cela M, Duchamp G, Palmer E (**2000**) Clinical studies on daily low dose oxytocin in mares at term. Equine Vet J 32: 307-10.

Chan LY, Fu L, Leung TN, Wong SF, Lau TK (**2004**) Obstetric outcomes after cervical ripening by multiple doses of vaginal prostaglandin E2. Acta Obstet Gynecol Scand 83: 70-74.

Chaudhuri S, Mitra SN, Biswas PK, Bhattacharyya S (**2006**) Premature rupture of membranes at term: immediate induction with PGE2 gel compared with delayed induction with oxytocin. J Obstet Gynecol India 56: 224-229.

Denison FC, Calder AA, Kelly RW (**1999**) The action of prostaglandin E2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. Am J Obstet Gynecol 180: 614-620.

Ferguson JE II, Ueland FR, Stevenson DK, Ueland K (**1988**) Oxytocin-induced labor characteristics and uterine activity after preinduction cervical priming with prostaglandin E2 intracervical gel. Obstet Gynecol 72: 739-745.

First NL, Alm CC (**1977**) Dexamethasone – induced parturition in Pony mares. J Anim Sci 44: 1072-1075.

Fowden AL, Forhead AJ, Ousey JC (**2008**) The Endocrinology of equine parturition. Exp Clin Endocrinol Diabetes 116: 393-403.

Hillman RB (**1975**) Induction of parturition in mares. J Reprod Fertil Suppl 23: 641-644.

Jeffcott LB, Rossdale PD (**1977**) A critical review of current methods for induction of parturition in the mare. Equine Vet J 9: 208-215.

Kelly RW (**1996**) Inflammatory mediators and parturition. Rev Reprod 1: 89-96.

LeBlanc MM (**1988**) Induction of parturition in the mare: significance of prepartum mammary secretions. Proc Soc Therio 85-88.

Ley WB, Bowen, JM Purswell, BJ Irby M, Greive-Crandell K (**1993**) The sensitivity, specificity and predictive value of measuring calcium carbonate in mares; prepartum mammary secretion. Theriogenology 40: 189-198.

Ley WB, Crisman MV, Jack NE (**1994**) Calcium carbonate content in pre-foaling mammary secretions and induction of foaling. Soc Theriogenol Proc 138-146.

Macpherson ML, Chaffin MK, Carroll GL, Jorgensen J, Arrott C, Varner DD, Blanchard TL (**1977**) Three methods of oxytocin – induced parturition and their effects on foals. J Am Vet Med Assoc 210: 799-803.

Martens RJ (**1982**) Evaluation of Neonatal Foal Distress. Comp Cont Educ Pract Vet 4: 23-34.

Meyers SA, LeBlanc MM (**1991**) Induction of parturition: Clinical considerations for successful foalings. Vet Medicine 86: 117-121.

Ousey JC, Dudan F, Rossdale PD (**1984**) Preliminary studies of mammary secretions in the mare to assess foetal readiness for birth. Equine Vet J 16: 259-263.

Pashen RL (**1980**) Low doses of oxytocin can induce foaling at term. Equine Vet J 12: 85-87.

Purvis AD (**1977**) The induction of labor in mares as a routine breeding procedure. In Proc 23rd Annu Conv AAEP, pp 145-160.

Rigby S, Love C, Carpenter K, Varner D, Blanchard T (**1998**) Use of prostaglandin E2 to ripen the cervix of the mare prior to induction of parturition. Theriogenology 50: 897-904.

Sennström MB, Ekman G, Westergren-Thorsson G, Malmström A, Byström B, Endresen U, Mlambo N, Norman M, Stâbi B, Brauner A (**2000**) Human cervical ripening, an inflammatory process mediated by cytokines. Mol Hum Reprod 6: 375-381.

Snegovskikh V, Park JS, Norvitz ER (**2006**) Endocrinology of parturition Endocrinol Metab Clin N Am 35: 173-191.

Stjernholm YM, Sahlin L, Eriksson HA, Byström BE, Stenlund PM, Ekman GE (**1999**) Cervical ripening after treatment with prostaglandin E2 or antiprogestin (RU486). Possible mechanisms in relation to gonadal steroids. Eur J Obstet Gynecol Reprod Biol 84: 83-88.

Vandeplassche M (**1980**) Obstetrician's view of the physiology of equine parturition and dystocia. Equine Vet J 12: 45-49.

Vandeplassche M (**1987**) The pathogenesis of dystocia and fetal malformation in the horse. J Reprod Fertil Suppl 35: 547-552.

Volkmann DH, Bertschinger HJ, Schulman ML (**1995**) The effect of prostaglandin E2 on the cervices of dioestrous and prepartum mares. Reprod Domest Anim 30: 240-244.

Witkowski M (**2007**) Observations on oxytocin-induced parturitions in mares. Med Weter 63: 209-212.