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Can Uterotonics Reduce Fetal and Newborn Piglet Mortality by Perinatal Asphyxia and Improve Functional Vitality?

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Stillbirths in large-scale porcine farms are still a problem reducing the reproductive performance. Oxytocin and vetrabutin chlorhydrate are the uterotonics frequently used with the purpose to accelerate the labor in sows of different countries, including Mexico. Currently, there is controversy if uterotonic drugs use increase or not the survival of the newly born porcine. The objective of this review is to comment the schemes of treatment used with oxytocin and vetrabutin chlorhydrate and their effects on mortality due to postnatal and intrauterine asphyxiation and discuss the uterotonics schemes of treatment that have tried to resolve it as well. We conclude that it is necessary to establish the pros and contrast of the use of oxytocin and vetrabutin chlorhydrate and the uterotonics treatment schemes to stop their indiscriminate use and overdosage because of a lack of standardized dose protocols, routes of administration and times of application during farrowing, which increase the risk of perinatal mortality.

Key words: Oxytocin, vetrabutin chlorhydrate, stillbirths, asphyxia, farrowing

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INTRODUCTION

In spite of the use of pharmacological products during the labor attendance, stillbirths in large-scale pig farms are still a great problem to solve in order achieve a high level of reproductive efficiency and survival (Mota-Rojas, 2005; Mota-Rojas *et al*., 2005a, b, c). Stillbirths in swine are classified in two types: type I or pre-partum stillbirths, with death of the newly born piglet (the term newly born refers specifically to the baby in the first minutes to hours following birth; in contrast, the neonatal period is generally defined as the first 28 days of life; (Kattwinkel *et al*., 1999) prior to the onset of parturition and are mainly due to an infectious disease; and type II (also referred to as intra-partum death), with death of the piglet during farrowing time, where death is generally not infectious in origin (Randall, 1972a; Curtis, 1974; Svendsen *et al*., 1986; Mota-Rojas *et al*., 2005a). Piglet mortality represents an important economic loss to the swine industry, approximately 40% of pre-weaning losses occur at birth and during the first day; 60% of these losses are due to physiologic farrowing failures (Randall, 1973), with nearly 80% of the stillbirths classified as type II (Leenhouwers *et al*., 2003). For normal farrowings, the rate of stillbirths ranges from 2 to 6% (Herpin *et al*., 1996; Lucia *et al*., 2002; Van der Lend and Van Rebs, 2003).

Perinatal asphyxia is a common cause of neonatal morbidity and mortality and neurologic disabilities among survivors. In addition to pulmonary, renal and cardiac dysfunction, hypoxic-ischemic encephalopathy develops in one third of asphyxiated newly born piglets (Nagdyman *et al*., 2001). Prolonged farrowing time has a great influence on the number of newborn pigs, mainly through asphyxia intra-partum (Randall, 1972a; Herpin *et al*., 1996; Lucia *et al*., 2002). Asphyxia or anoxia intra-partum or immediately post-partum is highly likely the most important cause of type II stillbirths in pigs (Randall, 1972a; Lucia *et al*., 2002). An increase in the tension of the umbilical cord during labor results in damage to the cord, increasing the risk of anoxia intra-partum and a high rate of perinatal mortality (Randall, 1972a). Although the piglet is considered a newborn relatively mature, it seems to be more susceptible to anoxia than other newborn animals (dogs, cats and rabbits) considered more immature (Curtis, 1974; Svendsen *et al*., 1986). Piglets have very low tolerance to anoxia caused by asphyxia and irreversible brain damage occurs during the 5 min subsequent to the rupture of the umbilical cord (Curtis, 1974; Handman *et al*., 1997).

Oxytocin (OT) is an uterotonic drug frequently used to decrease intra-partum mortality, as it shortens the duration of the farrowing and expulsion interval between successive newly born piglets (Straw *et al*., 2000). However, OT sometimes increases a little more the intensity and frequency of uterine contractions resulting in damage to umbilical cord (Linneen *et al*., 2005) and increases fetal mortality (Mota *et al*., 2002a; Alonso-Spilsbury *et al*., 2004).

There are also certain concerns regarding OT use, as oxytocin is thought to be the hormone most frequently misused in the farrowing barn. Misuse of this drug may cause farrowing complications and actually increase stillbirths. The dose of OT to be administered and the timing of the dose are highly controversial. This variation probably reflects the stage of gestation, state of luteolysis and whether milk let-down (closeness to 1st pig delivery). According to Straw *et al*. (2000), the total dose of OT in pre-parturient sows used in swine farms in the USA varies from 15 to 240 IU, which acts directly on the smooth muscle fibres and has no neurotropic activity. It has been used both experimentally and commercially in pigs, its activity is specific to the uterine body and cervical musculature; it acts on the myometrial cells, sealing off the membrane against the passage of potassium ions, thereby increasing membrane potential by lowering tonus. It also reduces the expulsion interval (between successive piglets) by up to 30% and therefore may enhance newborn piglet viability.

Vetrabutin Chlorhydrate (VC) is an uterotonic drug derivative of papaverine (Phillipp and Justus, 1992), which acts directly on the smooth muscle fibres and has not neurotropic activity, like OT it has been used both experimentally and commercially in pigs and its activity is specific to the uterine body and cervical musculature. It acts on the myometrial cells, sealing off the membrane against the passage of potassium ions, thereby increasing membrane potential by lowering tonus. VC reduces the expulsion interval to up to 30% and therefore may enhance piglet viability (EAEMP, 1999). Pigs are a Polytocous species so pigs born at the end of the litter are likely to suffer asphyxia to a greater degree due to the cumulative effects of the successive uterine contractions. These uterine contractions decrease oxygen to the fetuses and increase the risk of umbilical occlusion, damage or rupture of the umbilical cord, as well as a premature detachment of the placenta (Curtis, 1974). During this stage, there is a progressive bradychardia likely resulting from a failure of utero placental function, hypotension that decreases blood flow to vital organs leading to ischemia and severe hypoxia. Therefore, placental insufficiency plays a major role in the etiology of Intra-partum Deaths (IPDs) (Svendsen *et al*., 1991). Currently, there is controversy if the uterotonics VC and

OT used at farrowing can improve or not the survival of newly born piglets. The objective of this review is to comment the schemes of treatment frequently used with OT and VC in farrowing sows and their effects on mortality by postnatal and intrauterine asphyxiation, as well as the uterotonics schemes of treatment that have tried to resolve it and their indiscriminate use and overdosage due to a lack of standardized dose protocols, routes of administration and times of application during the farrowing time.

Intra-partum mortality in the pig farms: In spite of the pharmacological products used during farrowing, stillbirths in the pig industry continue being a problem. Fetal death is attributed to diverse causes and varies from 5-10% to 33.3% (Randall, 1972b; Borges *et al*., 2005).

Briefly, type I or ante-partum stillbirths have a rather characteristic edematous and hemorrhagic appearance, sometimes a grayish-brown discoloration due to early mummification and, if the process is advanced then the fetuses are dehydrated and lose hair. Type II or Intra-partum Stillbirths (IPS) have the exact appearance of their normal litter mates with the exception that they do not breathe; these pigs die of suffocation during parturition (Mota-Rojas *et al*., 2005a, c).

Type II stillbirths are generally associated with non-infectious etiology, depend on the farrowing duration (Randall, 1972a) and the premature rupture of the umbilical cord (Curtis, 1974; Mota *et al*., 2002b). When the farrowing time takes from 6 to 8 h, the incidence of stillbirths progressively increases (Randall, 1972a, b) moreover, from 1 to 8 h, the percentage of stilbirths by litter is increased from 2.4 to 10.5% (Sprecher *et al*., 1975) and 65% of these deaths occur in the last third of the litter (Svendsen and Bengtsson, 1986). Lucia *et al.* (2002) have shown that both duration of the farrowing and greater piglet´s weight are associated risk factors to neonatal mortality.

To evaluate the effect of the number of newborn piglets from a specific farrowing time, it is advisable to register the expulsion interval time between each newly born piglet to the birth. Piglets are born in an interval time of 16 min, which can vary from 12 to 18 min (Randall, 1972a, b; Fraser *et al*., 1997). Nevertheless, when a live piglet is born and subsequently there is expelled one dead piglet, the duration of the farrowing can extend 45 to 55 min. Although the expulsion interval is greater for the stillbirths, the dead fetuses *per se* are the cause of a prolonged parturition (Randall, 1972a).

Some studies have demonstrated that myometrial activity has an effect on the circulatory physiology and survival of the newborn pig. Uterine contractions cause a significant decrease in blood flow and gas exchange in the placenta leading to fetal hypoxia and other potentially deleterious effects to the newly born piglet (Tucker and Hauth, 1990). Most deaths at birth are due to a lack of oxygen, which occurs when the umbilical cord carrying oxygenated blood is twisted or ruptured (Randall, 1972b). However, this view has been challenged by other researchers (Herpin *et al*., 1996) who postulate that prolonged or intermittent asphyxia in utero and during delivery does not necessarily lead to IPS.

We and other researchers have shown a strong relationship between prolonged farrowing and type II stillbirth rates in pigs (Mota *et al*., 2002a, b). Stillborn rate increases from 2.4 to 10.5% when the farrowing time increases from 3 to 8 h. Svendsen *et al*. (1986), found that the number of stillborn pigs dramatically increased when the farrowing duration took more than 5 h. Delayed farrowing avoiding a normal newborn piglet breathing for 2 or 3 min, is a risk factor that significantly increases neonatal death. This form of death is frequently associated with laceration, puncture or compression of the umbilical cord caused by the pressure exerted by fetal or placenta tissues on the umbilical cord. Physical pressure on the umbilical cord reduces blood flow causing death due to hypoxia, or weakness and depression at the time of expulsion (Herpin *et al*., 1998). According to Randall (1972b) and Svendsen *et al.* (1986), 70 to 90% of stillborn pigs are born with ruptured umbilical cords or premature loosening of the fetal membranes.

Birth order and time interval between expulsions of two successive piglets are also key factors leading to porcine stillbirths (Alonso-Spilsbury *et al*., 2004). It has been documented that newly born pigs from the cervical end of the uterus are less likely to die during farrowing than those located toward the ovarian end of the uterus, which are expelled during the last phases of parturition. Studies have reported approximately 70-80% of intra-partum deaths in piglets expelled at the end of parturition (Randall, 1972a; Alonso-Spilsbury *et al*., 2005; Mota-Rojas *et al*., 2005a).

Vetrabutin chlorhydrate: VC is an uterotonic drug derived from the papaverine (Phillipp and Justus, 1992), it acts directly in fibres of the smooth muscle without neurotropic activity. It has been used in sows in both experimental and commercially ways, its activity is specific to the body of the uterus and cervical muscle. VC acts in the myometrial cells, closing the membrane and avoiding the ion passage potassium, due to this, the uterine tone increases the membrane potential. It also reduces the time interval between piglet expulsion >30% and therefore, it can increase newly born piglets viability (EAEMP, 1999).

Vetrabutin chlorhydrate used to decrease newborn pig mortality: In recent studies, we have shown that farrowing duration of treated-sows with VC (100 mg of VC per 60 kg of body weight) was 96 min smaller than the control group (Mota-Rojas *et al.*, 2005b) similar data was reported by Munnich *et al.* (1993), who found a reduction of 73 min in the duration of farrowing in VC treated-sows; however, this result differ with Phillipp and Justus (1992) because they observed a duration of the parturition of 411 min with the same dose between VC and control group. Moreover, Munnich *et al.* (1993) reported a significant reduction on newborn piglets death with the use of VC with respect to the control group. However, Mota-Rojas *et al.* (2005b) did not observe significant differences between the control and the VC-treated group.

In Mota-Rojas *et al.* (2005b) studies, the VC-treated group decreased both interval expulsion and duration of farrowing between-newly born piglets. Nevertheless, the use of OT increased intra-partum stillbirths, mainly due to umbilical cord rupture, whereas the VC treatment group modified in lesser degree, both uterine contraction intensity as well as frequency when it was compared with the oxytocin-treated group, leading to less severe umbilical cord changes, measured in terms of less ruptured and hemorrhagic umbilical cords. Moreover, VC reduced (33.4%) the IPS mortality rate in relation to oxytocin-treated group. Reports on human babies show intense asphyxia that produces artery pressure modifications, which makes the venous return (congestion) difficult, causing endothelial damage and lung and brain edema. If neonatal asphyxia persists, this may cause a vascular rupture, leading to brain-, lung- and endothelial hemorrhages.

Oxytocin synthesis: OT was the first peptide hormone to have its structure determined and the first to be chemically synthesized in biologically active form. The neurohypophysial OT and OT-like hormones facilitate reproduction in all vertebrates at several levels. The major site of OT gene expression is the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei. In response to a variety of stimuli such as suckling, parturition, or certain kinds of stress, the processed OT peptide is released from the posterior pituitary into the systemic circulation. Such stimuli also lead to an intranuclear release of OT. Moreover, oxytocinergic neurons display widespread projections throughout the central nervous system. However, OT is also synthesized in peripheral tissues, e.g., uterus, placenta, amnion, corpus luteum, testis and heart. The OT receptor is a typical class I G protein-coupledreceptor that is primarily coupled via Gq proteins to phospholipase C-β. The high-affinity receptor state requires both Mg^{2+} and cholesterol, which probably function as allosteric modulators (Gimpl and Fahrenholz, 2001). Both *in vivo* studies, mostly using uterine myometrial cells and transection studies with cloned oxytocin show that the oxytocin receptor functions primarily via a phospholipase C route leading to inositol trisphosphate (IP3) generation. In myometrial cells, the receptor is coupled by Gq and possibly Gi proteins to the phospholipase C, which via IP3 causes an increase in intracellular Ca^{2+} leading to muscle contraction. Production of IP3 parallels the increase in oxytocin receptor density, but Gq expression does not change; instead Gsa content, which is increased in pregnancy, mediating inhibition of contraction via cAMP and protein kinase A, falls at parturition (Blanks and Thornton, 2003). Thus, removal of inhibitory intracellular mechanisms may be more important in increasing myometrial sensitivity to oxytocin than is upregulating excitatory. All neurohypophysial hormones are nonapeptides with a disulfide bridge between Cys residues 1 and 6. This results in a peptide constituted of a six-amino acid cyclic part and a COOH-terminal α-amidated three-residue tail. The mature peptide products, OT and its carrier molecule neurophysin, are stored in the axon terminals until neural inputs elicit their release. The main function of neurophysin, a small (93-95 residues) disulfide-rich protein, appears to be related to the proper targeting, packaging and storage of OT within the granula before release into the bloodstream. OT is found in high concentrations (>0.1 M) in the neurosecretory granules of the posterior pituitary complexed in a 1:1 ratio with neurophysin have been demonstrated (Shyken and Petrie, 1995; Graves, 1996; Jianbo *et al.*, 2001; Petersson, 2002).

Recent studies have shown that RNAm of the OT is abundantly found in the sow´s endometrium and secretion of OT in great amounts within the uterine lumen, especially during gestation (Trout *et al.*, 1995). The main function of the OT is to act in the coordination of the uterine contractions of the farrowing time and in the phase of fetal expulsion (Gilbert *et al.*, 1994). Conversely, at the end of the farrowing time in some species, the levels of OT and OT mRNA are particularly low (Trout *et al.*, 1995).

Before the onset of labor, uterine sensitivity to OT markedly increases concomitant with a strong upregulation of OT receptors in the myometrium and to a lesser extent, in the decidua where OT stimulates the release of $PGF_{2\alpha}$. Experiments with transgenic mice suggest that OT acts as a luteotrophic hormone opposing the luteolytic action of $PGF_{2\alpha}$. Thus, to initiate labor, it might be essential to generate sufficient $PGF_{2\alpha}$ to overcome the luteotrophic action of OT in late gestation.

Oxytocin levels are elevated during farrowing since the pig endometrium synthesizes and releases great amounts of this hormone (Trout *et al*., 1995). The secretion of endogenous oxytocin during the farrowing is pulsating and these pulses are related to the fetal expulsion (Gilbert *et al*., 1994).

The physiological and biochemical mechanisms for regulation of endometrial PGF secretion during the estrous cycle in ruminants, especially sheep, have been extensively studied, but the mechanism(s) in swine has not received similar attention. OT stimulates phosphoinositide (PI) hydrolysis and prostaglandin $F_{2\alpha}$ (PGF) secretion differentially in Stromal Cells (SC), Glandular Epithelial Cells (GEC) and Luminal Epithelial Cells (LEC) isolated from porcine endometrium. Clearly, SC were most responsive and LEC were least responsive to OT for both PI hydrolysis and PGF secretion. Results from GEC were somewhat less consistent, but the responses of these cells were generally intermediate to those of SC and LEC. These results differ markedly from those using ruminant endometrium, in which responsiveness to OT resided entirely with epithelial cells and stromal cells were completely unresponsive, as OT receptor expression, as determined by *in situ* hybridization, appeared to be greater within the epithelium than within the stroma of porcine endometrium. It is not known if GEC and LEC would have been more responsive to OT if grown under polarizing conditions. The phospholipase C-mediated second messenger pathway is involved in OT-stimulated $PGF_{2\alpha}$ secretion from pig endometrium (Uzumcu *et al*., 1998).

Oxytocin stimulates PGE_2 release by rabbit amnion cells. This effect is mediated by OT receptors, which increase about 200-fold in rabbit amnion at the end of pregnancy. In view of the recent demonstrations that transgenic mice lacking either cytoplasmic phospholipase A_2, a key enzyme involved in PG synthesis, or PG receptors fail to deliver their offspring at term, amnion PGE_2 might play a critical role in the initiation of parturition in other species as well (Jeng *et al*., 1998).

Several recent studies have focused on a paracrine rather than endocrine regulation of myometrial contractility. The amnion and chorion are of fetal origin, metabolically active and located strategically adjacent to the decidua a maternal tissue in direct contact with the myometrium. Thus, the amnion, chorion and decidua are potential sources of paracrine regulators of myometrial contractility (Carvajal *et al*., 2001). When the uterus is prepared for farrowing, it is possible that the uterine activation occurs in response to a paracrin/autocrin action of a variety of uterotonics (Grammatopoulos and Hillhouse, 1999); oxytocin is the most powerful known endogen uterotonic agent (Fuchs and Fuchs, 1984).

Oxytocin vs. newly born pig mortality: In order to decrease intra-partum mortality, farrowings are commonly controlled with oxytocics (Pejsak, 1984); this drug has solved part of the problem by shortening farrowing duration and increasing the myometrial contraction. However, it can increase uterine contractions, diminishing blood flow to the uterus and gas exchange through the placenta (Tucker and Hauth, 1990). Recently, we and others have shown that oxytocics reduce the duration of farrowing but they do not decrease birth mortality (Gilbert, 1999; Mota *et al*., 2002b; Alonso-Spilsbury *et al*., 2004; Mota-Rojas, 2005; Mota-Rojas *et al*., 2005a, b, c).

OT is a drug used worldwide for induction and control of the farrowing (Mucio, 1996). Lucia *et al*. (2002) have shown that the OT treated-sows group during farrowing had a greater probability (20.8 times more) to have asphyxiated and dead newly born piglets than the non-treated group, if there is not synchronization between the moment of farrowing and the application of exogenous oxytocin, it can happen secondary uterine inertia, uterine atony and dystocia (Dial *et al*., 1987; Lunding-Schiller *et al*., 1996; Gilbert, 1999; Alonso-Spilsbury *et al*., 2004).

According to Mota-Rojas (2005) the application of oxytocin by intravenous (IV) injection causes a reduction of the uterine tone and delays expulsion time, with a greater number of IPDs and increasing the percentage of dead newly born piglets by meconium aspiration syndrome as a result of the hypoxia during farrowing. In this study intramuscular (IM) injection resulted in a greater period of hormonal activity, more born-alive piglets, smaller number of IPDs pigs with umbilical cord rupture and low fetal stress with respect to the IV route of administration.

Oxytocin contraindications: Oxytocin works directly as an uterotonic agent, specific receptors in the myoepithelial cells must be present. Premature uterine stimulation can interrupt the normal electromyographic patterns and it can also produce myometrial spasm, fatigue, distocia (Gilbert, 1999) and an increase in the manual attendance of the farrowing (Chantaraprateep *et al*., 1986; Dial *et al*., 1987; Alonso-Spilsbury *et al*., 2004). Additionally, the prolonged administration of oxytocin can lead to a decrease in the receptors regulation of the OT (Gilbert, 1999).

Oxytocics reduce the farrowing duration and fetus expulsion period. In case there is no synchronization between the stage of the farrowing and the application of exogenous OT or deficient ability of the sows's uterus to respond to the OT-treatment, it is important to know the side effects (Dial *et al*., 1987; Lunding-Schiller *et al*.,

1996). The sow is extremely sensitive to low doses of exogenous OT and the use of a single dose in gilts and adult females, may cause sows´ overdosage (Gadd, 1991). Likewise, it is important to know the course of the labor, therefore the use of this hormone is only recommended in those cases of primary uterine inertia (Gadd, 1991).

When a rupture of the umbilical cord occurs by excessive administration of oxytocics, there is severe asphyxiation and irreversible brain damage in the fetus (Curtis, 1974). At the cellular level, cerebral hypoxia-ischemia sets in motion a cascade of biochemical events commencing with a shift from oxidative to anaerobic metabolism (glycolysis), which leads to an accumulation of nicotinamide-adenine-dinucleotide (NADH), flavin-adenine-dinucleotide (FADH) and lactic acid plus H^+ ions. Anaerobic glycolysis cannot keep pace with cellular energy demands, resulting in a depletion of high-energy phosphate reserves, including ATP. Transcellular ion pumping fails, leading to an accumulation of intracellular Na^+, Ca^{++}, Cl^- and water (cytotoxic edema). Hypoxia-ischemia also stimulates the release of excitatory amino acids (glutamate) from axon terminals. The glutamate release in turn activates glutamate cell surface receptors, resulting in an influx of Na^+ and Ca^{++} ions. Within the cytosol, free fatty acids accumulate from increased membrane phospholipid turnover there after, undergo peroxidation by oxygen-free radicals that arise from reductive processes within mitochondria and as by-products in the synthesis of prostaglandins, xanthine and uric acid. Ca^{++} ions accumulate within the cytosol as a consequence of increased plasma (cellular) membrane influx through voltage-sensitive and agonist-operated calcium channels and of decreased efflux across the plasma membrane combined with release from mitochondria and the endoplasmic reticulum. Nitric Oxide (NO), a free-radical gas is generated via Ca^{++} activation in selected neurons and diffuses to adjacent cells that are susceptible to NO toxicity. The combined effects of cellular energy failure, acidosis, glutamate and NO neurotoxicity, free radical formation, Ca^{++} accumulation and lipid peroxidation serve to disrupt structural components of the cell with its ultimate death (Vannucci and Perlman, 1997).

Randall (1972a) and Sprecher *et al.* (1975) have reported that 93.6% of all newly born piglets deaths had intra-partum rupture of the umbilical cord during the farrowing and >80% of these deaths occurred in the third stage. Similarly, Svendsen *et al.* (1986) have shown that > 70% of the piglets with intra-partum dead, had rupture of the umbilical cord at farrowing. Alonso-Spilsbury *et al.* (2004) found that the intramuscular injection of high doses of oxytocin (equivalent to 0.167 UI kg^{-1} of body weight) in farrowing sows caused a greater number of stillbirths with ruptured umbilical cord and severe meconium staining. These previously results are in agreement with Mota-Rojas *et al.* (2005a), who have shown an increasing of approximately 2.5 more times of severe meconium staining piglets in the treated-group with high dose of oxytocin (0.167 UI kg^{-1} of body weight) compared with the treated-group with low dose (0.083 UI kg^{-1} of body weight). The higher number of alive-born piglets showing bradychardia, severe acidosis and meconium staining were from the oxytocin-treated group administered at birth of the first piglet; therefore the used dosage was not adequate treatment scheme in this study. The use of oxytocin-low dose helped to avoid the late decelerations of the fetal cardiac frequency, rupture of umbilical cord and skin meconium-staining; it also reduced the neonatal and fetal mortality and increased the neonatal viability and therefore its possibilities to survival. Oxytocin-low dose during the first and second labor stages caused more asphyxia and fetal deaths ($p<0.001$) and more side effects on piglet viability. Results from this study indicate that the best scheme for OT administration was lower doses through IM injection to promote uterine contractions, without fetal compromising and neonatal viability, administered after the birth of the eight piglet. IV-oxytocin administration and its lower action time showed more uterine atony, with a higher time of expulsion and a higher number ($p<0.01$) of IPS and also a higher number of meconium stained piglets at birth, with a severe meconium staining as a consequence of hypoxia during farrowing.

In the same study (Mota-Rojas *et al.*, 2005a), IM injection administration with a longer time action, favored a less number of IPDs and also, less IPDs with umbilical cord rupture and less number of animals with fetal suffering. The higher number of born-alive piglets showing bradychardia, severe acidosis and severe meconium staining in newly born piglets from sows treated with oxytocin indicate that the administration time (at birth of the first piglet) as well as the used dosage were not adequate treatment schemes. Oxytocin in low dose helped to avoid the late decelerations of the fetal cardiac frequency, rupture of umbilical cord and skin meconium-staining; it also reduced the neonatal and fetal mortality and increased the viability of the newly born piglet and increased its possibilities of survival. Oxytocin-low dose during the first and second labor stages caused more asphyxia and fetal deaths ($p<0.001$) and side effects on piglet viability. The results from this study indicated that the best time for oxytocin administration at lower dose, through IM injection to promote uterine contractions, without fetal compromising and neonatal viability was after the farrowing of the eight piglet.

DISCUSSION

In large-scale porcine farms stillborn rates have been reported from 5-10 to 31.3%; representing an important economic loss to the swine industry. We described above that approximately 40% of pre-weaning losses occur at birth and during the first day after birth; 60% of these losses are due to physiologic farrowing failures, with nearly 80% of the stillbirths classifed as type II. Birth order and time interval between expulsions of two successive newly born piglets are the mainly risk factors leading to porcine stillbirths.

Parturition results from a complex interaction of maternal and fetal factors. It requires that the uterus, which has been maintained in a relative state of quiescence during pregnancy, develops coordinated contractility and that the cervix dilates in a way that allows passage of the fetus through the birth canal. To be successful, parturition requires also that maturation of those fetal organ systems necessary for extrauterine survival had occurred and that the maternal organism had undergone the changes necessary for lactation in the postpartum period. It is not surprising, therefore, that synchronous maturation of the fetus and stimulus to increased uterine activity should be desirable and there is evidence suggesting that it is the fetus itself that triggers both series of events (Challis *et al*., 2000).

OT and VC are two of the uterotonics most frequently used with the purpose to accelerate labor in sows in different countries, including Mexico. The pregnant uterus is one of the traditional targets of uterotonics. OT is one of the most potent uterotonic agents identified and during late gestation, OT receptors are significantly induced in the myometrium in all mammalian species. Despite these associations, the physiological importance of OT in modulating the initiation and progression of labor remains unclear. Whereas OT infusion augments uterine contractions and hastens the progression of labor in both human and animal studies is not clear too. Nevertheless, the increase of uterine contractions decreases blood flow and gas exchange through the womb predisposing to intra-partum mortality. We previously reported (Mota-Rojas *et al*., 2006) that the administration of IV-oxytocin and its lower action time caused more uterine atony, with a higher expulsion time and a higher number ($p<0.01$) of intra-partum stillbirths and a higher number of meconium stained piglets during farrowing and severe meconium staining as a consequence of hypoxia than the controlled group. IM injection caused a less number of IPDs and also the less IPDs with ruptured umbilical cord and the number of animals with fetal suffering. According to the administration route of exogenous OT, application times, intensity and frequency of the myometrial contractions during farrowing, OT can change its effect.

The current trend to large-scale farms means that more and more pigs will spend their lives housed in intensive confinement systems. We and others have reported that oxytocin response may have a different response in the sows, depending on the type and conditions of housing system used at the farm (Lucia *et al*., 2002; Mota-Rojas, 2005).

The most obvious undesirable effect of umbilical cord disruption is stillbirth. A review of stillbirth literature from 1930-98 suggests that 15% of all stillbirths with an identifiable cause were associated with umbilical cord complications (Incerpi *et al*., 1998). Although difficult to prove in humans, umbilical cord complications are not uncommon in mammals, especially horses. Umbilical cord complications occur throughout pregnancy. Javert and Barton (1952) reviewed 1,000 cases of spontaneous abortion and reported that 56% had umbilical cord complications while controls had only 6%. These authors noted that most of the cord complications were such as to compromise the fetal circulation so as to cause death in utero. We also have shown that both OT and VC treatments reduced between-piglet expulsion interval and farrowing duration. Nevertheless, the use of OT increased intra-partum stillbirths, mainly due to umbilical cord rupture, whereas VC treatment modified, to a lesser degree, both contraction intensity as well as frequency (when compared to the oxytocin-treated group), causing less severe umbilical cord changes (in terms of less ruptured and less hemorrhagic umbilical cords). Moreover, VC reduced (33.4%) the IPDs mortality rate in relation to oxytocin treatment (Mota-Rojas *et al*., 2005b).

CONCLUSIONS

VC is quite used in porcine obstetrics, it is necessary to do more research studies with different treatment schemes with the purpose of evaluating different routes, dose and times of application to the farrowing of the sows in crates and pens and its effect on uterine dynamics, degree of asphyxia, acid-base imbalance, fetal mortality and newly born vitality. We conclude that it is necessary to establish the pros and contras of the use of OT and VC, as well as the uterotonics treatment schemes to stop their misuse and overdosage due to a lack of standardized dose protocols, routes of administration and times of application during farrowing, which increase the risk of perinatal mortality.

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