# Piglet vitality and mortality within 48h of life from farrowing sows treated with carbetocin, oxytocin or without intervention.

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# Contents

# Abstract

Stillborn piglets remain a major problem in intensive pig farming. To reduce mortality rates during birth process drugs are frequently used to decrease the length of the farrowing process. The aim of the present study was to compare piglet vitality and mortality within 48h of life when farrowing sows were treated with carbetocin, oxytocin or without intervention (control). Seventy-five (Camborough) and seventy-five (Topic 30) end of gestation sows from the first to the eleventh parity were used. Sows were housed in individual farrowing crates at two different intensive pig farms. The sows were randomly treated after the fourth piglet was born. Neonatal vitality was scored by judging piglets first breath, skin color, meconium staining and first standing resulting in a group of low vitality or high vitality score. Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) program. The binary logistic regression analysis was used to examine which variables had significant value in the present study. The variables farm and treatment were always included in the final model. Results showed treatment to have no significant influence on the piglet vitality score ($P>0.05$). Piglets of sows treated with carbetocin had also no significant effect on mortality within 48h of life ($P>0.05$) but piglets of sows treated with oxytocin were less likely to survive the first 48h of life ($P<0.05$). In conclusion, piglets born from oxytocin treated sows were less likely to live after the first 48h of life. Stillbirth rates did not deviated significantly between the different treatments. The present study recommend intensive pig farms not to use uterine contraction stimulating drugs on a routine basis for accelerating parturition after the fourth piglet is born.

# Introduction

Intensive pig farms target the number of weaned piglets per sow per year, in order to achieve the most profit. Herd productivity is influenced by litter size and pre-weaning mortality. Selection for higher litter size on pig farms is efficient, but prolongs the farrowing duration and often increases the number of stillborn piglets (Vanderhaeghe et al. 2010). Normal average interval between births of piglets amounts 16 min, varying from 12 to 18 min. After a live piglet is born, it can take about 45 to 55 min before a dead one is born, which also prolongs the farrowing time (Alonso-Spilsbury et al. 2004; van Dijk et al. 2005). Up to 8% of newborn piglets are stillborn, remaining a major problem in intensive pig farming (González-Lozano et al. 2010; Zaleski and Hacker 1993).

Drugs are frequently used in intensive pig farms to reduce piglet mortality by decreasing the length of birth process. Oxytocin is used in more than 80% of all pig farms in the United States and is characterized by stimulation of uterine contractions. Oxytocin reduces expulsion intervals between piglets and the overall duration of birth process (González-Lozano et al. 2010; Mota-Rojas et al. 2002; Mota-Rojas et al. 2005b). Administration of oxytocin 0,083 IU/kg body weight intramuscular (IM) after expulsion of the first piglet seems to decrease mortality rate and meconium staining significantly. (Mota-Rojas et al. 2005b). Another drug, carbetocin is also used to reduce mortality rate by decreasing expulsion intervals between piglets and the overall farrowing duration. Carbetocin seems to have a 3 times longer uterotonic activity and 25% greater contractile frequency compared to exogenous oxytocin in food-producing animals (Schramme et al. 2008). Neonatal piglet vitality score and mortality rates after administration of carbetocin during parturition are not yet known.

*Oxytocin*

Oxytocin is not only a drugs used in intensive pig farms, but is also a endogenous hormone functioning during lactation and the farrowing process (Zeeman et al. 1997). Unfortunately, birth process is still not fully understood (Lopez Bernal 2003; Shmygol et al. 2006). Although many other cascades play important roles in uterine contractions and labor, oxytocin may have a dual role in initiation of human labor. Zeeman et al (1997) suggests human labor initiation by acting directly on oxytocin receptor mediated and through voltage mediated calcium channels to stimulate uterine contractions, and indirectly through stimulation of amniotic and endometrial prostaglandin F2 alpha ($PGF_{2\alpha}$) and prostaglandin E2 ($PGE_2$) synthesis (Zeeman et al. 1997). Oxytocin is also used to induce parturition in at term mares, a similar direct action on the myometrium and indirect to the prostaglandin release is described. (Taverne and Noakes 2009)

In normal birth processes oxytocin is synthesized in the hypothalamus after a neurohumoral reflex, induced by peripheral stimuli such as stretching of the cervix and stimulation of the vagina and the nipple. Oxytocin is synthesized as a large precursor molecule that is rapidly broken down to the active hormone and its neurophysin before they are packed into neurosecretory granules. The neurosecretory granules are transported along the neurons into the posterior pituitary gland, also called neurohypophysis. Subsequently oxytocin and its neurophysin will be released in the blood by exocytosis (Soloff and Swartz 1974; Zeeman et al. 1997). Oxytocin circulates in the blood as a free peptide and is distributed into both the intravascular and extravascular compartments (Zeeman et al. 1997).

Oxytocin has a biological half-life of 4 to 10 minutes and a maternal metabolic clearance rate at term of 19 to 21 mL/kg/minute in human (Holleboom et al. 2013; Zeeman et al. 1997). On that account a continuous intravenous (IV) infusion or repeated intramuscular (IM) injections of exogenous oxytocin is required in human (Holleboom et al. 2013). Oxytocin is excreted in the urine, mainly in its biologically inactive configuration, which is formed after inactivation generally in the liver and kidney (Zeeman et al. 1997). So far porcine biological half-life of oxytocin are not published.

*Oxytocin receptors*

Myometrial oxytocin receptors are present in both non pregnant and pregnant human. The human oxytocin receptor is a polypeptide with 388 amino acids arranged in seven putative transmembrane domains and its cytoplasmic loops (Fig 1.). The receptor has a molecular weight of 43 kd and belongs to the G-protein coupled receptor (GPCR) family (Shmygol et al. 2006; Zeeman et al. 1997; Zingg and Laporte 2003). Rat oxytocin receptors in the myometrium are highest during parturition and in the mammary tissue during lactation. Partially because of the increase in oxytocin receptor concentration during human gestation, oxytocin binding in myometrium is 100-fold increased at term (Zeeman et al. 1997). Maternal serum oxytocin concentrations are not increased during early stages of human labor, so fetal oxytocin and perhaps local uterine and endometrium sources of oxytocin can act on their receptors (Zeeman et al. 1997). In sows, a pulse of oxytocin can be detected at the expulsion of each piglet (Blanks and Thornton 2003; Gilbert et al. 1994).

*Fig. 1*
*Human oxytocin receptor and interaction with oxytocin, Zingg, Laporte 2003*
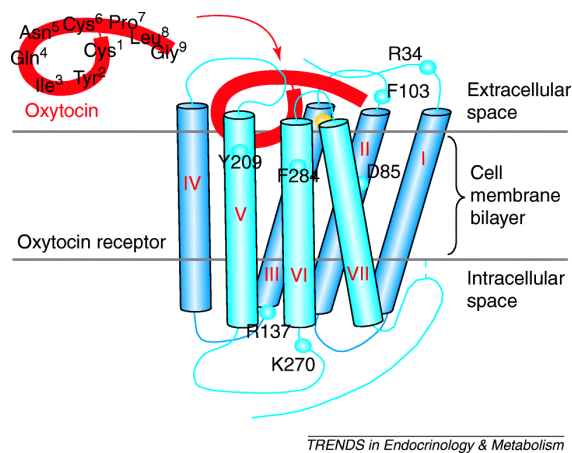


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Oxytocin receptors are coupled, after binding of oxytocin, through proteins of the $G_{q/11}$ family to phospholipase C β (PLC-β). This results in the formation of two second messengers: inositol 1,4,5-triphosphate ($IP_3$) and diacylglycerol (DAG). $IP_3$ releases calcium through specific receptors in the sarcoplasmic reticulum (SR) and DAG activates protein kinase C causing numerous effects (Lopez Bernal 2003; Shmygol et al. 2006). The release of calcium from the SR increases intracellular calcium concentration and will cause contraction. This calcium store depletes rapidly and calcium entry through the plasma membrane is needed to continue contraction (Lopez Bernal 2003).

Contraction of the myometrium consist of interaction between actin and myosin, regulated by the enzyme myosin light chain kinase (MLCK). When intracellular calcium concentration increases, calcium will bind to calmodulin and together they activate MLCK, which phosphorylates the myosin

light chains. The myosin light chains will interact with actin forming a complex capable of changing ATP into the mechanical energy of contraction (Lopez Bernal 2003).

Shmygol et al (2006) shows at least three different components on human uterine smooth muscles, seen in effect of oxytocin: 1. Increase in frequency of contractions; 2. Initial transient increase in the base tone (incomplete relaxation); and 3. Long-lasting increase in the amplitude and duration of phasic contractions (Shmygol et al. 2006).
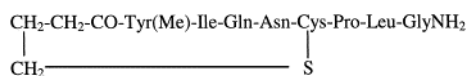
*Carbetocin*

Carbetocin binds with similar affinity to oxytocin receptors in the myometrium as oxytocin, resulting in rhythmic contractions, increased frequency of existing contractions and increased tone of the uterus.(Cordovani et al. 2012; Engstrøm et al. 1998; Su et al. 2012) Carbetocin is considered to reduce mean expulsion time of piglets and shortening farrowing time as well (Schramme et al. 2008).

Carbetocin is a synthetic octapeptide analogue of oxytocin, also given IV or IM (Cordovani et al. 2012; Su et al. 2012). Compared to oxytocin, carbetocin has some structural differences in the molecule. Fig. 2, 3 and 4 show the chemical structures of carbetocin and oxytocin by Engstrøm et al (1998). Although the chemical structures of carbetocin by Engstrøm et al (1998), Hunter et al (1992) and Schramme et al (2008) do not match, they all plead carbetocin to have more stability and avoid early decomposition compared to oxytocin. More stability of carbetocin is caused because of the replacement of the 1-6 disulfide bridge by a methylene group (Engstrøm et al. 1998; Hunter et al. 1992; Schramme et al. 2008). The biological half-life of carbetocin in human is 42 min, approximately four to ten times longer compared to oxytocin (Cordovani et al. 2012; Hunter et al. 1992). In pigs, a biological half-life of 85-100 minutes is documented for carbetocin (Schramme et al. 2008). Not only the plasma half-life of carbetocin is increased, but its lipophilic properties seems to cause a longer half-life at the receptor compartment as well (Hunter et al. 1992; Schramme et al. 2008).

*Fig. 2*
*Chemical structures of carbetocin and oxytocin, by Engstrøm, Barth et al. 1998*



**Carbetocin**

$CH_2$-$CH_2$-CO-Tyr(Me)-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH$_2$
$CH_2$ ——————————— S

**Oxytocin**

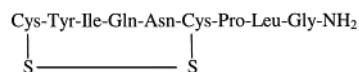Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH$_2$
S ——————————— S

*Fig. 3*
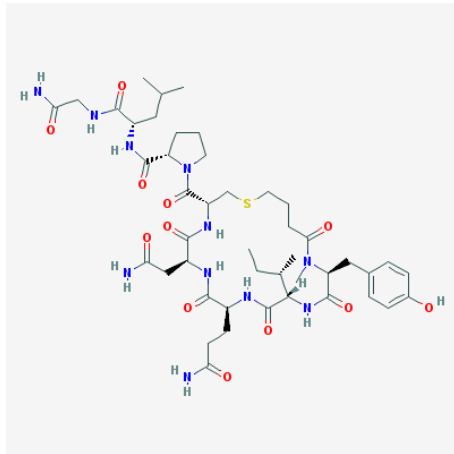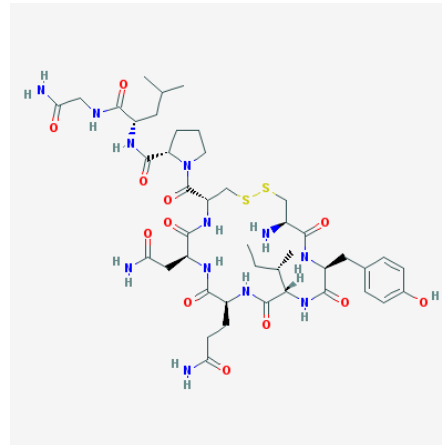*Chemical structures of carbetocin, Pubchem*



*Fig. 4*
*Chemical structures of oxytocin, Pubchem*

The main difference between carbetocin and oxytocin IM treatment is that carbetocin has a longer duration of action, and prolonged uterine response postpartum in terms of both amplitude and frequency of contractions (Su et al. 2012). Hunter et al (1992) suggests another difference between these two medicines, namely the decreased (one-tenth) potency of rat uterus in vivo to carbetocin compared to oxytocin (Hunter et al. 1992).

The administration of carbetocin compared to oxytocin is not the same in human. Carbetocin can be injected as a single dose instead of continuous IV infusion required for oxytocin in woman for preventing postpartum haemorrhage (PPH) after cesarean delivery (Cordovani et al. 2012). Su et al. (2012) claim titanic uterine contractions in less than 2 minutes after IM injection of carbetocin, lasting about 11 minutes, and followed by rhythmic contractions for about 2 hours in human. Intravenous carbetocin injections gives also titanic uterine contractions within 2 minutes, lasting 6 minutes, but followed by rhythmic contractions for only 1 hour (Holleboom et al. 2013; Hunter et al. 1992; Su et al. 2012). Intramuscular injection of carbetocin and oxytocin have relative lack of gastrointestinal and cardiovascular side-effects, but IM carbetocin injection is less invasive compared to IV oxytocin infusion in human (Su et al. 2007).

Carbetocin is not approved by the Food and Drug Administration (FDA) for use following vaginal births in human (Cordovani et al. 2012; Su et al. 2012). Although carbetocin is registered for sows being in parturition, no comparative study has yet been done between oxytocin and carbetocin on the vitality and mortality of piglets in porcine vaginal delivery.

*Negative effects*

Except for the benefits of oxytocin administration as described by Mota-Rojas et al (2002, 2005) and González-Lozano et al (2010), negative effects are described as well (González-Lozano et al. 2010; Mota-Rojas et al. 2002; Mota-Rojas et al. 2005b). Oxytocin (20-50 IU) was also reported to have a significant higher number of stillborn piglets per litter and a significant higher number of piglets with ruptured and haemorrhagic umbilical cords (Kaeoket 2006; Mota-Rojas et al. 2002; Mota-Rojas et al. 2005a). These uterotonic effects result in increased intrauterine hypoxia and stillbirths of piglets (Kaeoket 2006; Mota-Rojas et al. 2005a; Wehrend et al. 2005).

Hypoxia induces blood redistribution, increasing intestinal peristalsis and relaxation of the anal sphincter. Relaxation of the anal sphincter results in the expulsion of meconium into the amniotic fluid. Once in the amniotic fluid, the meconium stains the skin typical yellow. If hypoxia persists, fetuses gasp intra-uterine with open glottis, causing inhalation of amniotic fluid and meconium into their lungs (Mota-Rojas et al. 2012; Mota-Rojas et al. 2005b; Randall and Penny 1967).

Meconium is a viscous, greenish sterile substance present in the fetal intestine. It is a mixture of gastrointestinal secretion, bile, pancreas juice, mucus cellular detritus, amniotic fluid, vernix caseosa, lanugo and blood. Because hypoxia is needed for fetuses to defecate, the passage of meconium into the amniotic fluid is generally regarded as a good indicator of fetal distress (Mota-Rojas et al. 2012). Therefore, meconium staining of piglets indicates of intrauterine fetal distress (Alonso-Spilsbury et al. 2005; Alonso-Spilsbury et al. 2004; Kaeoket 2006; Mota-Rojas et al. 2002). Still, not all infants with fetal distress and meconium defecation into the amniotic fluid develop meconium aspiration syndrome (MAS). MAS is a significant cause of morbidity and mortality in fetuses and neonates. Meconium aspiration does not cause sufficient lung damage to kill an animal, but the animal will die because of systemic physiological abnormalities such as acidosis, hypertension and hypoxaemia (Mota-Rojas et al. 2012).

In the present study, the aim was to compare piglet vitality and piglet mortality within 48h of life, when farrowing sows were treated with oxytocin, carbetocin or without intervention (control). Two students are engaged in this research project; one student evaluates the effects on delivery duration and the other one evaluates piglet vitality and mortality within 48h of life. The purpose of the present study was to evaluate whether the application of carbetocin during parturition is more efficient regarding neonatal piglet vitality and mortality within 48h of life compared to oxytocin and control group.

# Material and methods

*Number of animals*

This study is performed at two commercial swine farms from November 2012 to January 2013. Farm 1 is located in the central area and farm 2 in the east area of The Netherlands. Two students observed 75 births on farm 1 or 75 births on farm 2. Camborough 29 sows on farm 1 were fed three times daily and had ad libitum access to water. Topic 30 sows on farm 2 were fed three times daily with commercial lactation liquid feed and had ad libitum access to water. Sows on both farms were moved into individual farrowing crates one week before the expected farrowing date and remained there until weaning. Approximately 100 sows littered on farm 1 through a three weeks schedule and 50 sows littered on farm 2 every week. Sow number, farm, gestation length and parity were reported when a sow started farrowing.

*Procedures*

Per farm sows were randomly arranged into three groups. In total each group included 50 sows. Many studies treated sows after expulsion from the first piglet (Alonso-Spilsbury et al. 2004; Mota-Rojas et al. 2002; Mota-Rojas et al. 2005a; Mota-Rojas et al. 2006). Yet Mota-Rojas et al (2007) showed administration with oxytocin late in labor to result in mild uterotonic effects but to be more efficient regarding fetal outcomes compared to administration at early phases of parturition (Mota-Rojas et al. 2007). On that account this study mediated and therefore decided to treat sows after expulsion of the fourth piglet. Sows of group L received 1 ml carbetocin (Longacton[®], 0,07 mg, Eurovet Animal Health) IM as advised in leaflet of Eurovet after the fourth piglet was born. Sows of group O received 1 ml oxytocin (Oxytocin[®], 10 IU, Eurovet Animal Health) IM also after expulsion of the fourth piglet. Sows of group C received no injection, but were observed without intervention. The study was set up triple blinded, the observers nor the statistician knew the contents of the bottles.

During the observations, sows and piglets were minimally assisted. Vaginal exploration was performed when birth interval between two consecutive piglets contained more than 45 minutes or occasionally earlier when intrauterine piglet were thought to have serious distress. Piglets born inside the membranes and weak piglets were assisted in respiration when needed and in suckling after 60 minutes. This study is approved by the Committee on Animal Experiments of Utrecht (DEC-number 2012.III.09.087).

*Experimental design*

In this study, 150 end of gestation sows were needed to observe parturition. Oxytocin and carbetocin solutions were injected with syringes and needles. Piglets were weighted and subsequently live born piglets were dried on their backs with tissues and a symbol for identification was painted on their back. After this procedure, piglets were placed back in the farrowing crates on the same place from where they were taken. At last permanent earmarks were given after the piglet had suckled for the first time or after 60 minutes. These permanent earmarks were needed to identify piglets dying within 48h of life.

*Live born piglets*

In human obstetrics, vitality of neonate babies is scored with the Apgar score. Heart rate, respiratory effort, reflex irritability, muscle tone and color are evaluated to predict survival(Rubarth 2012). Vitality of piglets was scored according to the scale of Zaleski and Hacker (1993) and modified by Mota-Rojas et al (2005), as used in the study of Gonzalez-Lozano et al (2009). This results in a score between 1 till 10 for each piglet (Gonzalez-Lozano et al. 2009; Mota-Rojas et al. 2005a; Trujillo-Ortega et al. 2007; Zaleski and Hacker 1993). In this study the time interval between birth and first breath, the snout skin color, the skin staining with meconium and the time interval between birth and first standing were used to evaluate live born piglet vitality (Table 1). Heart rate was not included because accurate counting was too difficult to perform. This results in a score between 0 till 8 for each piglet. Subsequently vitality is divided into two groups, the low vitality group(LVG) and the high vitality group (HVG). The LVG consist of piglets having a 1 to 5 vitality score and the HVG consist of piglets having a 6, 7 or 8 vitality score.

*Table 1*
*Viability of piglets scored according to this study.*

| Score | 0 | 1 | 2 |
|---|---|---|---|
| Time interval between birth and first breath | >1 min | 16 s – 59 s | <15 s |
| Snout skin color | Pale | Cyanotic | Pink |
| Skin staining with meconium | Severe | Mild | Absent |
| Time interval between birth and first standing | >5 min | 1-5 min | <1 min |

In addition head or breech presentation, umbilical cord rupture (broken, adhered different or adhered normal), intervention after 45 min, sex, birth order and weight of each piglet was noted. Piglets dying before 48h post-partum and their suspected cause of death were reported by the students, the farmer or his employees.

*Stillborn piglets*

Damage or rupture of the umbilical cord (UC), serial contractions, occlusion or placental detachment during parturition increase the possibility of piglets becoming stillbirths (González-Lozano et al. 2010). Stillbirths can be divided into two groups. Type I stillbirths contains death before parturition starts, often because of infectious causes. Type II stillbirths contains death during delivery and is often caused by non-infectious causes for example anoxia and dystocia (Alonso-Spilsbury et al. 2004; Mota-Rojas et al. 2002).

To classify stillbirth type I (pre-partum) and stillbirth type II (intra-partum) mortality criteria from Mota-Rojas et al (2006) were used, based on previous studies by Randall and Penny (1967), Sprecher et al (1974) and Svendsen et al (1986) (Mota-Rojas et al. 2006; Randall and Penny 1967; Sprecher et al. 1974; Svendsen et al. 1986). Type I stillbirths have characteristic edematous and hemorrhagic appearance and can be colored gray or brown because of autolysis and beginning mummification. Type I stillbirths were only analyzed on time born and head or breech presentation if seen. Type II stillbirths can be recognized because of their same appearance as their living littermates, but without breathing (Alonso-Spilsbury et al. 2004). Type II stillborns were evaluated on time born, head or breech presentation, umbilical cord appearance, skin staining with meconium, sex and weight. Mummies were excluded from this experiment, because injection during farrowing had no impact on them.

*Induction*

Pregnant sows require functional corpora luteal (CL), producing progesterone during their entire gestation. When the CL stops producing progesterone, also called luteolysis, pregnancy terminates and parturition starts. To synchronize parturition on farms, farrowing can be induced by a single IM administration of prostaglandin F2α (PGF$_{2α}$) or an analogue. Most sows will litter within 36 h after an IM injection at the manufacturer's label dose given at 112-114 days of gestation. Effective dose needed for inducing farrowing can be reduced by 25-50% of the IM dose when the vulva was injected (De Rensis et al. 2012).

Delivery on farm 1 was not induced. Farm 2 induced delivery by injection of 1 ml cloprostenol (Planate®, 0,0875 mg, Essex Animal Health Friesoythe), a PGF$_{2α}$ analogue, by vulval submucosal route. Injection was given every Thursday morning to at term sows, being ≥116 days of gestation. Kaeoket et al (2006) showed no significant effects of oxytocin (10 IU) administration IM 24h after farrowing induction with Preloban®, another PGF$_{2α}$ analogue, on the percentage of umbilical cord morphology and on the meconium staining degree (Kaeoket 2006). On that account, sows farrowing within 24h after cloprostenol injection were excluded from this experiment. To compare at least 4 piglets before and after treatment, sows with less than 8 born piglets were also excluded from this experiment.

*Statistical analysis*

To asses potential risk factors for the occurrence of the dependent variable high vitality score, a multivariable regression analysis was done. The multiple logistic regression was needed to compose the following regression line.

$$Y = a + b_1 x_1 + b_2 x_2 + b_3 x_3 + ... + b_i x_i$$

Variables ($x_1$, $x_2$, $x_3$, …) were pre-defined based on literature search on potential risk factors for low vitality score. Farm, treatment, head or breech presentation, umbilical cord rupture, intervention after 45 min, length of gestation, sex, induction, parity group, litter size, birth order and weight were used as independent variables (Table 2a). Independent variables were classified and these groups were compared with their standard group. Standard group consisted of piglets born alive in head presentation, in less than 45 min expulsion interval, with a normal umbilical cord, had not been induced nor treated with drugs and had a weight between 999 and 1500 g. In addition, male piglets born on farm 2, after an average gestation length on that farm, from a sow of second, third, fourth or fifth parity with more than 14 piglets and born between a birth order of 5 till 8 were chosen to be statistically standard as well.

In all analysis, backward-stepwise elimination of non-significant variables was applied to the variables of interest. The variables farm and treatment were always included in the final models, because differences in farm management cannot be neglected and treatment differences were examined in this study. Statistical analysis were carried out with the Statistical Package for the Social Sciences (SPSS) program. For all analyses, a *P* value less than 0.05 was considered statistically significant.

To start a backward logistic regression analysis for mortality within 48 h of life, the same independent variables were used as in the analysis of vitality, but vitality was also included as

independent variable (Table 2b). Farm, treatment, litter size and intervention were potential risk factors used in the backward logistic regression analysis of the dependent variable stillbirth (Table 2c).

*Table 2a*
*Dependent (Y): vitality group and independent (X) variables used for backward LR*

| Variable, $Y$ | Numerical value of $Y$ |
|---|---|
| Vitality group (discrete) | Low vitality group= 0, High vitality group= 1 |
| **Variable, $x_i$** | **Numerical value of $x_i$** |
| Farm (discrete) | Farm 2= 0, Farm 1= 1 |
| Treatment (discrete) | No intervention= 0, Carbetocin= 1, Oxytocin = 2, |
| Head or breech presentation (discrete) | Head= 0, Breech= 1, Unknown= 2 |
| Umbilical cord rupture (discrete) | Normal= 0, Broken= 1, Adh. Different = 2 |
| Intervention (discrete) | No intervention= 0, Intervention after 45min= 1 |
| Gestation length – average gestation length (discrete) | Average gest. length= 0, 2 days before= 1, 2 days after= 2, 1 day before= 3, 1 day after= 4 |
| Sex (discrete) | Male= 0, Female= 1 |
| Induction (discrete) | Not induced= 0, Induced= 1 |
| Parity (discrete) | 2-5 parity= 0, 1 parity= 1, >5 parity= 2 |
| Litter size (discrete) | >14 piglets= 0, 8-10 piglets= 1, 11-14 piglets= 2 |
| Birth order (discrete) | Piglet 5-8= 0, Piglet 9-12= 1, Piglet >12= 2 |
| Weight (discrete) | 1000-1499 g=0, <1000 g= 1, >1499 g= 2 |

*Table 2b*
*Dependent (Y): mortality group and independent (X) variables used for backward LR*

| Variable, $x_i$ | Numerical value of $x_i$ |
|---|---|
| Farm (discrete) | Farm 2= 0, Farm 1= 1 |
| Treatment (discrete) | No intervention= 0, Carbetocin= 1, Oxytocin = 2, |
| Head or breech presentation (discrete) | Head= 0, Breech= 1, Unknown= 2 |
| Umbilical cord rupture (discrete) | Normal= 0, Broken= 1, Adh. Different = 2 |
| Intervention (discrete) | No intervention= 0, Intervention after 45min= 1 |
| Gestation length – average gestation length (discrete) | Average gest. length= 0, 2 days before= 1, 2 days after= 2, 1 day before= 3, 1 day after= 4 |
| Sex (discrete) | Male= 0, Female= 1 |
| Induction (discrete) | Not induced= 0, Induced= 1 |
| Parity (discrete) | 2-5 parity= 0, 1 parity= 1, >5 parity= 2 |
| Litter size (discrete) | >14 piglets= 0, 8-10 piglets= 1, 11-14 piglets= 2 |
| Birth order (discrete) | Piglet 5-8= 0, Piglet 9-12= 1, Piglet >12= 2 |
| Weight (discrete) | 1000-1499 g=0, <1000 g= 1, >1499 g= 2 |
| Vitality group (discrete) | Low vitality group= 0, High vitality group= 1 |

*Table 2c*
*Dependent (Y): stillbirths and independent (X) variables used for backward LR*

| Variable, $Y$ | Numerical value of $Y$ |
|---|---|
| Stillbirths (discrete) | Stillbirths type II= 0, Live born piglets= 1 |
| **Variable, $x_i$** | **Numerical value of $x_i$** |
| Farm (discrete) | Farm 2= 0, Farm 1= 1 |
| Treatment (discrete) | No intervention= 0, Carbetocin= 1, Oxytocin = 2, |
| Intervention (discrete) | No intervention= 0, Intervention after 45min= 1 |
| Litter size (discrete) | >14 piglets= 0, 8-10 piglets= 1, 11-14 piglets= 2 |

# Results

From the 150 parturitions observed in this study, 2121 piglets were born alive (92.0%), 183 were stillbirths (8.0%). Sows ($n$ = 150) used in this study had a parity ranged from 1 till 11, with a mean of 4.39. These sows had litters between 8 and 25 piglets, with an average of 15.36 piglets. Mean weight at birth for live born piglets ($n$ = 2121) was 1295.21 g, ranging from 292 till 2461 g. Stillbirths type II average birth weight ($n$ = 141) was 1005.99 g, ranging from 339 till 1992 g. Other descriptive statistics are presented in Table 3.

*Table 3*
*Mean ± Std Error (SE), Minimum (Min), Maximum (Max) values.*

|  | Mean ± SE | Min | Max |
|---|---|---|---|
| Parity | 4.39 ± 0.19 | 1 | 11 |
| Parity group L (Longacton) | 4.32 ± 0.30 | 1 | 9 |
| Parity group O (Oxytocin) | 4.52 ± 0.35 | 1 | 10 |
| Parity group C (Control) | 4.34 ± 0.34 | 1 | 11 |
| Litter size | 15.36 ± 0.27 | 8 | 25 |
| Litter size group L | 15.56 ± 0.48 | 8 | 25 |
| Litter size group O | 15.18 ± 0.47 | 9 | 22 |
| Litter size group C | 15.34 ± 0.46 | 8 | 23 |
| Weight of live born piglets | 1295.21 ± 7.29 | 292 | 2461 |
| Weight of live born piglets group L | 1297.50 ± 13.32 | 480 | 2461 |
| Weight of live born piglets group O | 1292.81 ± 12.59 | 292 | 2266 |
| Weight of live born piglets group C | 1295.35 ± 11.97 | 365 | 2048 |
| Weight of stillbirth type II | 1005.99 ± 31.99 | 339 | 1992 |
| Weight of stillbirth type II group L | 1009.43 ± 47.66 | 380 | 1848 |
| Weight of stillbirth type II group O | 966.59 ± 64.94 | 339 | 1807 |
| Weight of stillbirth type II group C | 1042.03 ± 57.25 | 451 | 1992 |

Piglet one till four were excluded from this experiment, because treatment occurred after expulsion of the fourth piglet. Stillbirth type I piglets were also excluded because treatment did not affect these piglets. Two piglets had both male and female genitals, these piglets (sex 2) were excluded from this experiment as well. Therefore the measurements of 1540 piglets born alive (92.2%) and 130 stillbirths (7.8%) were used. Group L contained 564 born piglets (33.8%), with 509 live born piglets (90.2%) and 55 stillbirth type II (9.8%). Group O contained 553 born piglets (33.1%), with 514 live born piglets (92.9%) and 39 stillbirth type II (7.1%). Group C contained 553 born piglets (33.1%), with 517 live born piglets (93.5%) and 36 stillbirth type II (6.5%) (Table 4).

*Table 4*
*Frequency piglets died and lived within 48h of life*

| Piglets | Born | Born alive | Stillbirth type II | Died | Lived |
|---|---|---|---|---|---|
| Group L | 564 | 509 | 55 | 53 | 456 |
| Group O | 553 | 514 | 39 | 56 | 458 |
| Group C | 553 | 517 | 36 | 33 | 484 |
| Total | 1670 | 1540 | 130 | 142 | 1398 |

Mean weight at birth for live born piglets starting from piglet number 5 ($n$ = 1540) was 1300.40 g, ranging from 292 till 2461 g. Stillbirths type II average birth weight starting from piglet number 5 ($n$ = 129) was 1012.44 g, ranging from 339 till 1992 g. Other descriptive statistics are presented in Table 5.

*Table 5*
*Mean ± Std Error (SE), Minimum (Min), Maximum (Max) values without piglet 1-4 and sex 2*

|  | Mean ± SE | Min | Max |
|---|---|---|---|
| Weight of live born piglets | 1300.40 ± 8.622 | 292 | 2461 |
|   Weight of live born piglets group L | 1298.83 ± 15.797 | 494 | 2461 |
|   Weight of live born piglets group O | 1301.67 ± 15.170 | 292 | 2266 |
|   Weight of live born piglets group C | 1300.68 ± 13.822 | 365 | 2070 |
| Weight of stillbirth type II | 1012.44 ± 33.888 | 339 | 1992 |
|   Weight of stillbirth type II group L | 1009.07 ± 51.884 | 380 | 1848 |
|   Weight of stillbirth type II group O | 977.69 ± 67.244 | 339 | 1807 |
|   Weight of stillbirth type II group C | 1055.14 ± 59.380 | 451 | 1992 |

Considering stillbirths type II (stillbirths(0) vs live born piglets(1)) as dependent variable, the multivariable model ended with litter size and intervention as independent variables after backward logistic regression. Since this study examines the relation between the application of different medicines to piglets vitality score, farm and treatment had to stay in the model. The final model contained the independent variables: farm, treatment, litter size and intervention (Table 6). Farm and treatment had no significant influence on stillbirth rates. Piglets born after vaginal exploration had a lower odds ratio (0.16) with respect to live born piglets without intervention (*P*<0.05). Piglets born in litters of 11 till 14 piglets had a higher odds ratio (2.10) compared to piglets born in litters of more than 14 piglets with respect to live born piglets (*P*<0.05). This was also seen for piglets born in litters of 8-10 groups (4.55), but not being significant.

*Table 6*
*Binary Logistic Regression; dependent (Y): stillbirths*

| Variable, $x_i$ | Numerical value of $x_i$ | $b_i$ | SE ($b_i$) | *P*-value | Estimated odds ratio | 95% for odds ratio |
|---|---|---|---|---|---|---|
| Farm (discrete) | Farm 2= 0, Farm 1= 1 | -0.155 | 0.202 | 0.445 | 0.857 | 0.576-1.274 |
| Treatment (discrete) | No intervention= 0 |  |  | 0.629 |  |  |
|  | Carbetocin= 1 | -0.166 | 0.245 | 0.497 | 0.847 | 0.524-1.368 |
|  | Oxytocin = 2 | 0.039 | 0.257 | 0.880 | 1.039 | 0.628-1.720 |
| Litter size (discrete) | >14 piglets= 0 |  |  | 0.006 |  |  |
|  | 8-10 piglets= 1 | 1.514 | 1.018 | 0.137 | 4.546 | 0.619-33.411 |
|  | 11-14 piglets= 2 | 0.739 | 0.254 | 0.004 | 2.095 | 1.274-3.443 |
| Intervention (discrete) | No intervention= 0, Intervention after 45min= 1 | -1.810 | 0.276 | 0.000 | 0.164 | 0.095-0.281 |
| Constant | *a* | 2.333 | 0.366 | 0.000 | 10.304 |  |

After backward logistic regression of the dependent vitality group, the model contained 4 variables: head or breech presentation, umbilical cord rupture, birth order and weight. The other variables farm, treatment, intervention, gestation length, sex, induction, parity and litter size were eliminated from the model. Since this study examines the relation between the application of different medicines to piglets vitality score, the final model contained the independent variables: farm, treatment, head or breech presentation, umbilical cord rupture, birth order and weight (Table 7).

Oxytocin had a higher odds ratio (1.06) with respect to high vitality of piglets born in the group no intervention and carbetocin had a lower odds ratio (0.78) compared to the no treated vitality group (Table 7). However these differences were not significant. Concluding, in this study treatment had no significant effect on the piglet vitality score.

*Table 7*
*Binary Logistic Regression, dependent (Y): vitality*

| Variable, $x_i$ | Numerical value of $x_i$ | $b_i$ | SE ($b_i$) | P-value | Estimated odds ratio | 95% for odds ratio |
|---|---|---|---|---|---|---|
| Farm (discrete) | Farm 2= 0, Farm 1= 1 | -0.132 | 0.167 | 0.432 | 0.877 | 0.632-1.217 |
| Treatment | No intervention= 0 | | | 0.238 | | |
| (discrete) | Carbetocin= 1 | -0.249 | 0.194 | 0.200 | 0.780 | 0.533-1.141 |
| | Oxytocin = 2 | 0.060 | 0.204 | 0.770 | 1.061 | 0.711-1.584 |
| Head or breech | Head= 0 | | | 0.003 | | |
| presentation | Breech= 1 | -0.524 | 0.166 | 0.003 | 0.592 | 0.428-0.819 |
| (discrete) | Unknown= 2 | 0.502 | 0.531 | 0.344 | 1.652 | 0.584-4.674 |
| Umbilical cord | Normal= 0 | | | 0.000 | | |
| rupture (discrete) | Broken= 1 | -0.685 | 0.187 | 0.000 | 0.504 | 0.349-0.728 |
| | Adh. Different = 2 | -0.852 | 0.294 | 0.004 | 0.427 | 0.240-0.759 |
| Birth order | Piglet 5-8= 0 | | | 0.000 | | |
| (discrete) | Piglet 9-12= 1 | 0.055 | 0.209 | 0.792 | 1.057 | 0.701-1.593 |
| | Piglet >12= 2 | -0.622 | 0.194 | 0.001 | 0.537 | 0.367-0.786 |
| Weight (discrete) | 1000-1499 g= 0 | | | 0.070 | | |
| | <1000 g= 1 | -0.401 | 0.205 | 0.050 | 0.669 | 0.448-1.001 |
| | >1499 g= 2 | -0.351 | 0.189 | 0.063 | 0.704 | 0.486-1.019 |
| Constant | $a$ | 1.831 | 0.200 | 0.000 | 6.242 | |

Piglets with a weight less than 1000 g and more than 1499 g both had a lower odds ratio (0.67 and 0.70 respectively) with respect to high vitality of piglets born with a weight between 1000 and 1500 g. Although these groups of weight were not significant, the group piglets with a weight less than 1000 g was almost significant (Table 7).

The statistical analysis of these results also showed that the high vitality score was strongly influenced by all umbilical cord rupture classes. Broken and adhered different umbilical cords both had a lower odds ratio (0.52 and 0.39 respectively) with respect to vitality of the group piglets born with normal umbilical cords (*P*<0.05). So both classes were less likely to score high vitality compared to the normal umbilical cord group. On that account, a backward LR was also done with umbilical cord rupture (abnormal(0) vs normal(1)) as dependent variable and head or breech presentation, intervention, treatment, induction, birth order and litter size as independent variables. The final model contained the two variables head or breach presentation and birth order (Table 8).

Breech presentation had a lower odds ratio (0.92) with respect to piglets born with normal umbilical cords in the head presentation group, suggesting piglets born in breech presentation to be less likely to have a normal umbilical cord, but this was not significant (Table 8). Concluding, no relation was seen with umbilical cord rupture and piglets born in breech presentation. In contrast birth order groups 9-12 and >12 had significantly lower odds ratio (0.59 and 0.49 respectively) with respect to umbilical cords of piglets born in the birth order 5-8 (*P*<0.05). Assuming piglet groups born later in gestation (>8) were less likely to have normal umbilical cords (Table 7).

*Table 8*
*Binary Logistic Regression, dependent (Y):  umbilical cord*

| Variable, $x_i$ | Numerical value of $x_i$ | $b_i$ | SE ($b_i$) | P-value | Estimated odds ratio | 95% for odds ratio |
|---|---|---|---|---|---|---|
| Head or breech | Head= 0 | | | 0.096 | | |
| presentation | Breech= 1 | -0.084 | 0.129 | 0.512 | 0.919 | 0.714-1.183 |
| (discrete) | Unknown= 2 | 0.691 | 0.352 | 0.049 | 1.996 | 1.002-3.976 |
| Birth order | Piglet 5-8= 0 | | | 0.000 | | |
| (discrete) | Piglet 9-12= 1 | -0.532 | 0.149 | 0.000 | 0.587 | 0.439-0.786 |
| | Piglet >12= 2 | -0.707 | 0.150 | 0.000 | 0.493 | 0.367-0.662 |
| Constant | $a$ | 1.329 | 0.123 | 0.000 | 3.778 | |

Of the 1540 piglets born alive, 142 piglets died in the first 48h of life and 1398 piglets lived after the first 48h of life. Regarding mortality within the first 48h of life as dependent variable, the backward LR model contained the variables treatment and weight at the last step. Because farm had to remain in the model, the final model contained: farm, treatment and weight. Of these variables farm had no significant effect. The independent variable weight was significant for all subgroups. Piglets born with a birth weight of less than 1000 g had a lower odds ratio (0.10) with respect to mortality of piglets with a weight between 1000-1499 g (*P*<0.05). Piglets born with a birth weight starting from 1500 g had a higher odds ratio (3.63) with respect to mortality of piglets with a weight between 1000-1499 g (*P*<0.05). Concluding, in piglets there is a significant correlation between weight and mortality within 48h of life.

Treatment with carbetocin and oxytocin both had a lower odds ratio (0.63 and 0.53 respectively) with respect to piglet mortality within the first 48h of life in the control group (Table 9). However the odds ratio of oxytocin was significant, but the odds ratio of carbetocin was not significant. Concluding, a significant effect between oxytocin treatment and piglet mortality within 48h of life. Oxytocin treated piglets were less likely to survive the first 48h of life compared to control piglets.

*Table 9*
*Binary Logistic Regression; dependent (Y): mortality within 48 h of life*

| Variable, $x_i$ | Numerical value of $x_i$ | $b_i$ | SE ($b_i$) | P-value | Estimated odds ratio | 95% for odds ratio |
|---|---|---|---|---|---|---|
| Farm (discrete) | Farm 2= 0, Farm 1= 1 | 0.030 | 0.195 | 0.876 | 1.031 | 0.704-1.509 |
| Treatment | No intervention= 0 | | | 0.038 | | |
| (discrete) | Carbetocin= 1 | -0.456 | 0.250 | 0.068 | 0.634 | 0.388-1.034 |
| | Oxytocin = 2 | -0.631 | 0.250 | 0.012 | 0.532 | 0.326-0.868 |
| Weight (discrete) | 1000-1499 g= 0 | | | 0.000 | | |
| | <1000 g = 1 | -2.308 | 0.209 | 0.000 | 0.100 | 0.066-0.150 |
| | >1499 g= 2 | 1.290 | 0.445 | 0.004 | 3.633 | 1.520-8.683 |
| Constant | $a$ | 2.702 | 0.155 | 0.000 | 14.912 | |

These results indicate no significant correlation between treatment and vitality score and no significant correlation between treatment and stillbirths. In contrast, a significant correlation is found between treatment and mortality within 48h of life. Piglets born in the oxytocin treated group were less likely to live after the first 2 days of life compared to the not treated group (*P*<0.05).

# Discussion

Application of carbetocin or oxytocin during parturition did not influence vitality of piglets, because no significant effect was found in the present study. Mota-Rojas et al (2005) showed oxytocin to cause intrauterine fetal asphyxia (Mota-Rojas et al. 2005a). Fetal asphyxia causes reduced vitality in piglets that survive the birth process (Herpin et al. 1996; Kammersgaard et al. 2011; Kirkden et al. 2013; Trujillo-Ortega et al. 2007). All fetuses cope with moderate hypoxia, because uterine contractions decrease uteroplacental blood flow (Mota-Rojas et al. 2005b). Approximately 14% of all live born piglets score low postnatal vitality due to decreased fetal blood flow and oxygen during birth (Mota-Rojas et al. 2012).

Mota-Rojas et al (2012) showed severe meconium staining at birth to associate with low neonatal vitality score and meconium staining occurred regularly when the umbilical cord has been ruptured (Mota-Rojas et al. 2012). From the 81 born alive stained piglets (BASP) in the article of Mota-Rojas et al (2005) 37.4 % of the group piglets treated with an IM saline solution and 80.6% of the group piglets treated with an IM oxytocin application showed a delayed inspiration more than 15 s after birth. Pale and cyanotic skin frequency was also greater in the oxytocin treated group compared to the saline treated group ($P$<0.01) (Mota-Rojas et al. 2005a). Because interval between birth and first breath, meconium staining and skin color were used in the vitality score of the present study, uterine stimulation with oxytocin was expected to decrease vitality score of neonatal piglets. In addition carbetocin was thought to increase the piglet vitality score because of its prolonged duration and diminished potency of action compared to exogenous oxytocin (Hunter et al. 1992; Su et al. 2012).

The results in this research could be explained because Mota-Rojas et al (2005) used 1 IU/6 kg live weight after expulsion of the first piglet instead of 10 IU/sow after expulsion of the fourth piglets in the present study (Mota-Rojas et al. 2005a). Compared to the articles of Mota-Rojas et al (2005) and Wehrend et al (2005), 10 IU oxytocin given IM in this study had not increased intrauterine hypoxia of piglets (Mota-Rojas et al. 2005b; Wehrend et al. 2005). The action of 1 mg carbetocin is equivalent to that of 50 IU oxytocin (Schramme et al. 2008). So 0,07 mg carbetocin used in this study is equal to 3,5 IU oxytocin and on that account did not increase intrauterine hypoxia of piglets nor change the vitality score.

Stillbirth rates had no significant effect according to the treatment groups, this is in accordance with other studies (Kaeoket 2006; Kirkden et al. 2013). After excluding the first four piglets born, the carbetocin group had 9.8% type II stillbirths, the oxytocin group contained 7.1% type II stillbirths and the control group contained 6.5% type II stillbirths. The control group had the lowest percentage of stillbirths type II, which could be interpret as being the most efficient group, although not being significant.

It could be considered whether decreased possibility of piglets to survive the first 48h of life when their moms were treated with oxytocin could be explained through the moment of treatment. Mota-Rojas et al (2007) showed oxytocin treatment (0.083 IU/kg) after expulsion of the eighth piglet, to have 68% fewer piglets stained with meconium than controls. Treatment after expulsion of the fourth piglet, took about 28% more piglets stained with meconium than controls. They concluded oxytocin administration at early phases of parturition to result in increased duration and intensity of uterine contractions, subsequently decreasing placenta perfusion and producing adverse fetal

outcomes (Mota-Rojas et al. 2007). In the present study, sows were treated after expulsion of the fourth piglet. Future research should prove whether treatment with oxytocin and carbetocin after the expulsion of the eighth would improve piglet vitality.

In conclusion, neonatal piglet vitality was not significantly changed by sow treatment with 10 IU oxytocin or 0.07 mg carbetocin after expulsion of the fourth piglet in the present study. In this study piglets born from sows treated with oxytocin were less likely to survive the first 48h of life in respect to the control group ($P<0.05$). Because oxytocin treatment showed a significant elevation of mortality within 48h of life and carbetocin treatment showed no improving vitality score or survival rate after 48h of life in this study, carbetocin is not valued to be more efficient regarding neonatal vitality and mortality within 48h of life compared to oxytocin and control group. The present study advises farmers not to use any uterine contraction stimulating drugs during parturition on a routine basis after the fourth piglets is born.

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