



Influence of prenatal maternal corticosteroid therapy on clinical and metabolic features and pulmonary function of preterm newborn puppies



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ABSTRACT

Although the effects of antenatal corticosteroid therapy in clinical improvement and pulmonary maturation in preterm have been described, little is known on premature newborn puppies. This study aimed to evaluate the effect of maternal administration of a single dose of prenatal betamethasone on lung function of preterm newborn puppies in the first hours of life, especially from the clinical point of view and acid-base balance. A prospective study was conducted involving 21 puppies allocated into three experimental groups: Term Group (63 days post-ovulation), Preterm-Treated Group (57 days post-ovulation and maternal administration of a single dose of 0.5 mg/kg of betamethasone) and Preterm-Control Group (57 days post-ovulation). Puppies were analyzed clinically through the Apgar score, heart rate, respiratory rate and neurological tests (muscular tone and irritability reflex) and for oximetry and blood acid-base balance in distinct experimental moments. Premature puppies had marked degree of prematurity, reversed by maternal administration of betamethasone. Prenatal corticosteroid therapy promoted better pulmonary and metabolic condition, with more efficient compensatory response to acid-base imbalance and better pulmonary gas exchange capacity. Therefore, prenatal treatment with betamethasone can be adopted as clinical lung maturation protocol for pregnancies at risk in order to prevent low vitality and increase neonatal survival.

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1. Introduction

Maturation of fetal respiratory system begins during intrauterine life and extends to postnatal period, under the influence of various endocrine factors [1]. Increased production of fetal cortisol at the end of pregnancy is among these factors, acting in the regulation of pulmonary, renal, liver and gastrointestinal development in preparation to postnatal life [2].

The use of synthetic corticosteroids during the prenatal period aiming to artificially induce fetal lung maturation began in 1972 after a pioneering study with preterm lambs by Liggins and Howie [3]. The same results were further confirmed in systematic studies in lambs [4], calves [5], rabbits [6], monkeys [7] and humans [8,9]. During the last decades, treatment with synthetic glucocorticoids

24–48 h before delivery in women with gestational risks has been routinely used with the primary objective of fetal lung maturation [1]. This procedure showed significant reduction in the incidence of Neonatal Respiratory Distress Syndrome [9,10] and the marked reduction of morbidity and mortality in preterm human neonates [11]. Despite the undoubted beneficial effect of corticosteroids on the development of vital organs of the fetus, drug action is dose [12], delivery time and species dependent [13]. In pregnant cows or sheep, exogenous synthetic glucocorticoids cross the placental barrier and act similarly to cortisol in late pregnancy, stimulating fetal maturation [13,14]. However, significant results in improving lung function are observed only when delivery occurs in an interval from 2 to 7 days after administration [13]. In medicine, it is recommended the use of a single cycle, with two applications of 12 mg of betamethasone with 24-h intervals [15]. In single dose, it was also possible to identify lung maturation in sheep neonates [12]. For this purpose, the preparation of disodium betamethasone phosphate (soluble and readily absorbed) and betamethasone acetate

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(which acts as deposit) is recommended as drug of choice to promote improved neonatal lung function [15].

Although the effects of antenatal corticosteroid therapy in clinical improvement and structural and functional maturation of the lung parenchyma in preterm human [16], lamb [17] and calves [5] have been described, little is known about the effect on premature newborn puppies. The time period between drug application and birth, as well as the optimal dose to be applied were not determined for pregnant bitches, resulting in the empirical use of antenatal corticosteroid therapy. The interest in the advancement of perinatal procedures in dogs is due to the high reported neonatal mortality rates [18,19]. Especially for certain dog breeds (terriers and brachycephalic), there is higher risk of complications during delivery, as well as maternal metabolic and respiratory disorders in late pregnancy, which often require emergency interventions and pregnancy interruption.

Thus, this study aimed to evaluate the effect of maternal administration of a single dose of prenatal betamethasone on the lung function of preterm newborn puppies in the first hours of life, especially from the clinical point of view and acid-base balance.

2. Material and methods

The use of animals in the present study was approved by the Ethical Committee of the School of Veterinary Medicine and Animal Science - University of São Paulo (protocol no. 1672/2009).

2.1. Animals and experimental design

A prospective study was conducted involving 21 neonatal puppies, of distinct genders, born from primiparous and pluriparous bitches ($n = 6$). All females were mongrels, aged from 1 to 6 years and body weight varied from 15 to 25 kg. Bitches were healthy by the time of the study, free of anatomic or reproductive disorders, and were fed a commercial diet for dogs. All bitches were privately owned and for ethical reasons only females not intended for reproductive purpose were assigned to the present experiment. Additionally, only bitches to which the owners desired to perform ovariohysterectomy were elected. All owners signed a written informed consent prior to entering the study and were aware of the pregnancy interruption, surgical and anesthetic risks and agreed with the gonadectomy.

The estrous cycle (proestrus and estrus) was accurately monitored every other day for artificial insemination timing based on complete gynecological examination (clinical evaluation, vaginal cytology and vaginoscopy). When the transitional period between proestrus and estrus was identified, a daily follow-up was performed using the following parameters: vaginal cytology – females were considered in estrus when: 1) the colpocytological exam resulted in 90% of superficial cells; 2) vaginoscopy – with the use of a pediatric proctoscope (WelchAllyn®), the onset of estrus was diagnosed whenever the vaginal mucosa appeared pale, with an evident primary folding and secondary wrinkling. Ovulation timing corresponded to the intensification of secondary folding or crenulation; 3) serum progesterone assay, using radioimmunoassay previously validated for dogs. The LH peak was estimated when the progesterone concentration reached between 1 and 1.9 ng/mL.

In order to obtain preterm puppies, pregnancy was interrupted on the 57th day of gestation, based upon estimation of ovulation, which was considered to occur 48 h after the LH surge. Artificial insemination using a single mongrel male was performed in all bitches on days 1, 3 and 5 after ovulation.

Pregnant bitches were arbitrarily allocated in three experimental groups, according to the corticosteroid treatment and gestational age in which pregnancy interruption was performed:

Term Group: puppies born from pregnancies with 63 days post-ovulation ($n = 7$)

Preterm-Treated Group: puppies born from interrupted pregnancies with 57 days post-ovulation ($n = 7$). Maternal administration of a single dose of 0.5 mg/kg of maternal body weight of betamethasone (Celestone Soluspan®, Merck & Co., Inc., Whitehouse Station, NJ, USA), IM, was performed at 55 days post-ovulation;

Preterm-Control Group: puppies born from interrupted pregnancies with 57 days post-ovulation ($n = 14$). Maternal administration of saline solution (0.9% NaCl) in an equal volume of betamethasone was performed at 55 days post-ovulation.

In order to homogenize obstetrical condition at birth, all bitches were subjected to caesarian section with the following anesthetic protocol: acepromazine (0.02 mg/kg) with tramadol (2 mg/kg) for tranquilization, IM. For anesthetic induction, we used slowly IV injection of propofol (1 mg/kg), epidural blockage with lidocaine (2 mg/kg) and morphine (0.1 mg/kg). After hysterotomy and fetal removal, isoflurane in inhalatory anesthesia was used for maintenance, according to the protocol determined by Oliva [20].

2.2. Neonatal analysis

Immediately after birth, all fetuses had their fetal membrane removed and the amniotic fluid drained from nasal surface. Simultaneously to neonatal drying, vigorous thoracic massage was employed as neonatal resuscitation procedure. Puppies were maintained in a neonatal incubator with a radiant warmer (articulate reflector) and adjustable temperature at 30–33 °C (Berço Aquecedor AQ50®, Fanem, São Paulo, Brazil), which allowed implementation of the experimental procedures. Neonatal analysis was performed chronologically at the following order: Apgar score assessment, clinical analysis and body temperature, oximetry and blood hemogasometric analysis.

Neonates were physically examined through Apgar score for neonatal vitality [21] at birth and at 5 min (5 min after the previous evaluation). To establish the Apgar score, we evaluated the heart (A) and the respiratory rates and effort (B) through pulmonary auscultation. Furthermore, the muscle tone (C) of each neonate was evaluated mainly by observing the puppies's ability to maintain a dorsal recumbency position; their head movements were also evaluated. An irritability reflex (D) was estimated from the neonate's responsiveness to manipulation during the examination. Finally, the colors of the mucous membranes (E) of the gums were inspected to verify the presence of pallor or cyanosis. For each variable (A-E), a punctuation of 0, 1 or 2 was given, and the final sum score (0–10) was established.

For overall clinical analysis at 60 min, 120 min and 240 min after birth, puppies were examined for heart rate (HR), respiratory rate (RR) and neurological tests [muscular tone (MT) and irritability reflex (IR)]. Muscular tone was graded on an arbitrary scale of 0–2, being 0- the total lack of tonus (flaccidity); 1- partial head flexion in dorsal recumbence; and 2- complete head and limb flexion with a body posture resembling the C letter. Irritability reflex was also graded on an arbitrary scale of 0–2, being 0- the total lack of motor or vocal response to the interdigital reflex; 1- slow response to the interdigital reflex; and 2- marked motor and vocal response to the interdigital reflex.

In order to analyze blood oxygenation through the percentage of hemoglobin bound to oxygen (Hb-O₂), we performed a non-invasive peripheral pulse oximetry (Oximax N85®, Nellcor, EUA) with the oximetry sensor placed at the femoral artery topography (medial hindlimb). Oximetry was performed at punctual moments during the experimental period (240 min) and results were

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