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Effect of maternal metabolism on fetal supply: Glucose, non-esterified fatty acids and beta-hydroxybutyrate concentrations in canine maternal serum and fetal fluids at term pregnancy

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ABSTRACT

The progressive adaptations in carbohydrate and lipid metabolism during canine pregnancy are reflected in the concentrations of glucose, non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHB). The levels of these metabolites in the bitch likely affect fetal concentrations and the composition of amniotic and allantoic fluids (AMF and ALF, respectively). We studied 31 canine parturitions (Cesarean sections) and found that glucose, NEFA and BHB concentrations were significantly higher in maternal serum than in AMF or ALF. Glucose levels in maternal serum, AMF and ALF were closely related ($R^2 \geq 0.821$, $P < 0.0001$) as well as serum and AMF BHB levels ($R^2 = 0.661$, $P < 0.0001$). In maternal serum, increases in NEFA were associated with increased BHB, and both were negatively related to glucose ($P \leq 0.010$). To estimate the effect of the metabolic burden of pregnancy, we evaluated these variables in relation to the dam's body weight and to the ratio of litter weight to the dam's body weight (LW/BW). Maternal serum glucose was not influenced by LW/BW, but it was lower in small than in large/giant bitches. Small breed dogs and those with > 10% LW/BW had significantly higher serum NEFA and BHB concentrations. Glucose in AMF and ALF was independent of LW/BW ($P \geq 0.399$). AMF NEFA was lower and BHB higher, if LW/BW was > 10% ($P \leq 0.048$). In conclusion, the extent of the metabolic load of pregnancy in bitches depends on breed size and on the ratio of litter weight to dam's body weight. Maternal concentrations of glucose, BHB and NEFA determine the concentrations of these metabolites in fetal fluids.

1. Introduction

During canine pregnancy, maternal hormonal changes and metabolic strategies accommodate for increasing fetal nutrient requirements. Progesterone, estradiol, leptin, thyroid hormones, cortisol, insulin and growth hormone are all involved in the progressive adaptation of maternal energy metabolism to fetal needs (Concannon, 1986; Johnson, 2008; Thuroczy et al., 2016; Cardinali et al., 2017). This, in turn, results in impaired insulin actions e.g. decreased expression and phosphorylation of insulin receptor substrate-1, suppression of the insulin-dependent glucose transporter 4 translocation to the plasma membrane, and thereby reduced insulin sensitivity in skeletal muscle and adipocytes (Feldman and Nelson, 2004; Batista et al., 2005; Connolly et al., 2007; Johnson, 2008; Wada et al., 2010; Strage et al., 2014). Peripheral insulin sensitivity in the bitch is already reduced by day 35 of pregnancy and becomes more severe (~40% decrease) in late gestation (Concannon, 1986; Connolly et al., 2007). This reduced insulin sensitivity

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causes a relative intracellular energy deficiency, that is, lower glucose utilization in maternal peripheral tissues (Johnson, 2008) to ensure sufficient glucose supply to the fetus(es). It also enables maternal lipid mobilization and increased hepatic ketogenesis (Johnson, 2008). Although insulin resistance is a normal feature of pregnant as well as non-pregnant diestrous dogs (Concannon, 1986; Strage et al., 2014), it constitutes a risk factor for diabetes mellitus (DM), which is a common endocrine disorder in dogs (Feldman and Nelson, 2004; Rand et al., 2004; Nelson and Reusch, 2014). Still, despite the even more pronounced insulin resistance in pregnant compared with non-pregnant diestrous bitches (Concannon, 1986), gestational DM in dogs is rare (Norman et al., 2006; Fall et al., 2008; Fall et al., 2010; Armenise et al., 2011).

Metabolic adaptations of pregnancy, such as increased hepatic glucose output, decreased peripheral insulin sensitivity, unchanged hepatic insulin sensitivity and lower peripheral insulin levels, allow the dam to maintain euglycemia (Connolly et al., 2000; Connolly et al., 2007) and to support fetal growth despite the increasing nutritional demands. However, the counter-regulatory responses of glucagon and norepinephrine are suppressed during gestation (Connolly et al., 2004), which makes it more difficult for pregnant bitches to cope with hypoglycemia. Therefore, if fetal nutrient demands are too high (i.e., large litter) or the nutrient supply of the dam is insufficient, pregnancy toxemia (ketosis) may develop, which is characterized by persistent hypoglycemia, increased adipose tissue release of non-esterified fatty acids (NEFA) and production of ketone bodies (Johnston et al., 2001; Johnson, 2008). Insufficient nutrient supply in the form of a carbohydrate-restricted diet during gestation resulted in significantly increased NEFA and β-hydroxybutyrate (BHB) concentrations and lower plasma glucose levels the week before whelping (Romsos et al., 1981). Some bitches had glucose concentrations as low as 0.8–1.1 mmol/L within two days before whelping, and they were lethargic and did not take care of their pups after parturition. Acute hypoglycemia in pregnancy toxemia may result in even more severe clinical signs in the dam including weakness, ataxia, collapse, seizures and coma (Johnson, 2008).

The consequences of these metabolic alterations in the bitch may be life threatening to the pups in extreme cases, for instance, only 63% of the puppies were born alive from the carbohydrate-restricted bitches compared with 96% live-born pups in the control dams (Romsos et al., 1981). The extent to which changes in the concentrations of glucose, NEFA and BHB immediately after birth in the puppies themselves could have contributed to their mortality was not investigated (Romsos et al., 1981). It should be considered that NEFA and BHB can cross the placenta, as shown in women, and serve as nutrient sources to the fetus (Berghaus et al., 1998; Herrera and Ortega-Senovilla, 2014). Essential and long-chain polyunsaturated fatty acids, a small portion of which is transported through the placenta from circulating maternal NEFA, are indispensable for normal fetal growth and development, while BHB is an alternative energy source, in particular for the fetal brain, when glucose, the primary energy substrate is limited, and it can also be used for lipid synthesis (Kalhan et al., 1997; Herrera, 2002; Ward Platt and Deshpande, 2005; Herrera and Ortega-Senovilla, 2014). Although neither newborn blood glucose nor BHB levels measured within 8 h after birth were predictive of puppy mortality (Mila et al., 2017), glucose concentrations in fetal amniotic fluid (AMF) were significantly lower in puppies dying within 48 h of birth than in those that survived (Groppetti et al., 2015). Another research group studying NEFA levels in canine fetal fluids found higher concentrations in small than in medium and large size bitches (Meloni et al., 2014), supporting that small size dams and perhaps also their fetuses have higher degree of lipolysis. Ketone bodies, which are indicative of the extent of lipolysis and ketogenesis, were also detected in term canine fetal fluids using a semi-quantitative test (Balogh et al., 2017).

The origin of fetal fluids also determines their biochemical composition. The AMF directly surrounds the embryo or the fetus within the amnion membrane (Leiser and Kaufmann, 1994). In human pregnancy, after formation of the placenta and fetal vessels, it is mainly the fetal plasma, but also the permeable surfaces of the amnion, placenta and umbilical cord, which determine AMF composition before keratinization of the fetal skin (Li et al., 2005; Underwood et al., 2005). After the fetal skin is keratinized, urine of human fetuses is the main contributor to AMF. Secretions of the fetal respiratory tract, oral cavity and gastrointestinal tract also modify AMF content, while its removal occurs mostly by intramembranous pathway, by fetal swallowing, and to a smaller extent by transmembranous pathway (Brace, 1995; Ross and Nijland, 1997; Underwood et al., 2005; Jellyman et al., 2009; Anderson et al., 2013). In contrast to humans, in which the allantois regresses (Leiser and Kaufmann, 1994), in species like the dog, it expands and allantoic fluid (ALF) accumulates within the allantoic or allantochorionic membrane surrounding the amnion (Leiser and Kaufmann, 1994). ALF is primarily derived from fetal urine. As pregnancy advances and the urachus is progressively occluding, urine enters the amniotic cavity in greater amounts. ALF composition is also modulated by placental, trans- and intramembranous pathways (Mellor and Slater, 1971; Brace et al., 1992; Brace, 1995; Shandley et al., 1997; Li et al., 2005). Although the exact mechanisms regulating AMF and ALF composition in the bitch are not known, several biochemical parameters were different between these two fetal fluids at term pregnancy, e.g. specific gravity, bilirubin, calcium, magnesium and some of the liver enzymes were lower in AMF than in ALF (Balogh et al., 2017; Veronesi et al., 2018). Furthermore, higher creatinine, urea and potassium content in ALF may suggest fetal urine draining into the allantoic cavity (Veronesi et al., 2018).

In dogs, maternal serum levels together with the biochemical composition of fetal fluids have not yet been reported, so it is not clear to what degree fetal fluid concentrations of some carbohydrate and lipid metabolites, i.e., glucose, NEFA and ketone bodies, are influenced by maternal concentrations. The goal of our study was therefore to investigate the relationships among glucose, BHB and NEFA concentrations in maternal serum and fetal AMF and ALF of parturient bitches undergoing Cesarean section (C-section). Furthermore, to estimate the effect of the physical and metabolic burden of pregnancy, we evaluated the concentration of these metabolites in relation to the dam's body weight (BW) as well as in relation to the ratio of the weight of the litter to the bitch's body weight (LW/BW, %).

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