

ULTRASOUND LOCAL HEATING IMPROVE FOETAL PHYSIOLOGICAL DEVELOPMENT IN MATERNAL HYPERPARATHYROIDISM

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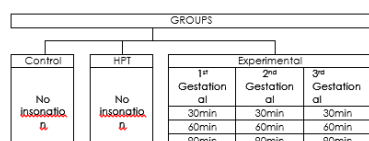
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Graphical abstract



Abstract

Parathyroid disorder associated with hypercalcemia during pregnancy reduces the normal foetal growth, skeletal mineralization and serum calcium concentration. Hypercalcemia increases the risk of birth loss and foetal postpartum complications which includes intrauterine growth retardation, low birth weight, preterm delivery, neonatal hypocalcaemia, tetany and still-birth. Human and animal study exhibit benefits from local hyperthermia induced by ultrasound exposure. Ten-month-old primiparous New Zealand White (NZW) does were assigned into three different groups; control (C), healthy NZW does and free from ultrasound insonation; hyperparathyroidism (HPT), a positive control group having hypercalcemia conditions established through administering phosphate intravenously for 5 months and free from parathyroid ultrasound insonation; treatment (T), an experimental group experiencing hypercalcemia condition and receiving parathyroid ultrasound insonation during pregnancy as intervention to hyperparathyroidism. In treatment group rabbit were exposed for 30, 60 and 90 minutes of parathyroid ultrasound exposure on 1st, 2nd and 3rd gestational stage accordingly. Following birth, foetal serum calcium (SCa), body weight (BW), crown-to-rump length (CRL), total body length (TBL), biparietal diameter (BPD) and femur length (FL) of the foetal were measured. Maternal hypercalcemia during pregnancy produced small to gestational age (SGA) progeny with significant reduction of BW, CRL, TBL, BPD, FL and SCa compared to normal. While the outcome of ultrasound exposure given during middle 2nd gestational stage resulted in significantly increase in progeny mean average BW, CRL, TBL, BPD FL and SCa compared to HPT group. Ultrasound induced local heating demonstrated an improved in the physiological development of progeny in the cases of maternal hypercalcemia condition.

Keyword: Hypercalcemia, parathyroid ultrasound, intrauterine retardation, physiological

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1.0 INTRODUCTION

Parathyroid hormone (PTH) played a decisive role in maintaining calcium homeostasis. Disturbance in parathyroid hormone results in abnormal serum calcium concentration. Hyperparathyroidism (HPT) is a parathyroid disorder that caused unregulated overproduction of parathyroid hormone (PTH) resulting in high serum calcium concentration. HPT, considered a benign disease of the elderly but it can

be a life – threatening disease if it occurs during pregnancy [1]. HPT during pregnancy is not a common disease, however it is no longer considered a rare disease because there has been a great increase in the incident rate in recent years [1] with 25% of HPT cases are diagnosed in woman during their child bearing age [2].

Parathyroid disorder during pregnancy can cause serious problems to the mother as well as the unborn baby if left untreated. Maternal and neonatal

complications due to HPT during pregnancy has been reported as high as 67% and 80% respectively [1]. Risk of miscarriages are 3-5 folds higher than expected as it usually occur in late first trimester or early second trimester and recurrent miscarriage is likely to occur [3, 4]. In human study, miscarriages can be detected at all elevated calcium levels but frequently seen in cases of calcium levels exceeding 2.85mmol/l [3].

Maternal hypercalcemia during pregnancy expose the unborn foetal to intrauterine hypercalcemia suppressing the development of foetal parathyroid glands with consequent predisposition to life threatening foetal postpartum early-onset hypocalcemic crisis [5]. It has been reported that even mild hypercalcaemia in the mother can cause neonatal parathyroid suppression [6]. The inability of the immature parathyroid gland to supply sufficient PTH to adapt to the abrupt disconnection of umbilical cord caused sudden loss of placenta calcium supply at birth [7]. Previous report stated that moderate or severe maternal HPT develop babies with severe calcium deficiency or permanent hypoparathyroidism in worse cases [8] associated with other complications including intrauterine growth retardation, low birth weight, preterm delivery, neonatal hypocalcaemia, tetany and still-birth [3, 4].

Currently, surgery is the most common treatment for primary HPT but pregnancy seems to be a hindrance. Nearly all of the cases reported suggest that parathyroidectomy during late 2nd trimester or early 3rd trimester will reduce the anesthesia risk to the infant and claimed to be safe for both mother and baby [3]. Parathyroidectomy performed in the third trimester of pregnancy is effective and decrease maternal and foetal complication [9]. Unfortunately, pregnancy loss usually occurs during late 1st trimester or early 2nd trimester [3]. Human study [3] reported that pregnancy loss occur between the 7th and 23rd week of gestation (average 12.2 ± 4.5 week) but the risk is increased to six folds during the second trimester. Therefore prior to parathyroidectomy, surgery carried out during late 2nd trimester will put more pregnancies at the risk of lost. Furthermore, few miscarriage cases have been reported while waiting for the late 2nd trimester. It was previously reported that the clinical significant complication of HPT during pregnancy if left undiagnosed or delay diagnosed caused death ranging from 17.6% to 23.5% in foetal and 18.8% to 25.0% in the mother [10].

Previous human and animal study show benefits from local hyperthermia induced by ultrasound exposure. Human study discovered that ultrasound heating decrease PTH levels and the sizes of parathyroid tumours [11, 12], while animal study show reduction in tumor volume after ultrasound intervention as a treatment [13]. The present study will compare the outcome of ultrasound insonation as intervention in maternal HPT associated hypercalcemia condition in relation to foetal

intrauterine growth and serum calcium concentration.

2.0 MATERIALS AND METHODS

The research protocol was approved by University's Committee on Animal Research & Ethics and all experiments were carried out in Laboratory Animal Facility and Management, Faculty Pharmacies, UiTM.

Ten-month-old primiparous New Zealand White (NZW) does were assigned to 3 major groups (Figure 1) based on their serum calcium concentrations; control (C), healthy NZW does and free from ultrasound insonation; hyperparathyroidism (HPT), a positive control group established through administering phosphate intravenously for 5 months [14] and free from parathyroid ultrasound insonation; treatment (T), having hypercalcemia condition which were established through administering phosphate intravenously for 5 months and receiving parathyroid ultrasound insonation during pregnancy as intervention to hyperparathyroidism.

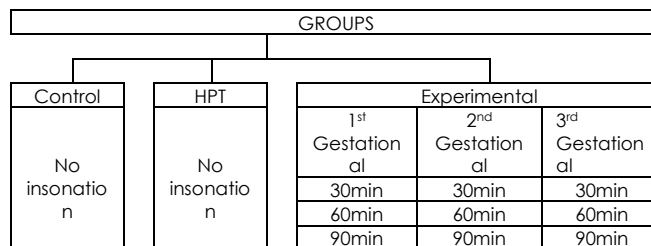


Figure 1 Chart of ultrasound insonation given according to groups

The Treatment group were then further divided into 3 different groups according to gestation periods namely 1st gestation, 2nd gestation and 3rd gestation based on the time of ultrasound insonation given during pregnancy (Figure 1). Each rabbit received ultrasound insonation once for 30 minutes, 60 minutes and 90 minutes in the middle of the gestational stage accordingly.

All does were mated with normal and healthy NZW buck. The average gestational term for rabbit ranged between 30-33 days [15] and consists of three stages. Following birth, the foetal were euthanized using diethyl ether and the foetal body weight, foetal longitudinal growth parameter which includes crown-to-rump length (CRL), total body length (TBL), foetal biometric parameter include Bi-parietal diameter (BPD), femur length (FL) and foetal serum calcium (SCa) biochemistry were measured. Femoral bone were dissected and placed in 10% buffered formalin. Foetal BW were weighed using 6R-202 AND analytical balance. CRL were measured using vernier scale while, the TBL were measured using standard measuring tape. Micro-computed tomography

(micro-CT) was used to measure the BP and the femur length. . Litters blood was withdrawn via cardiac puncture and were analysed at the Faculty of Veterinary Medicine Universiti Putra Malaysia.

Result from experimental group were compared with the control and HPT groups to evaluate the effect of ultrasound intervention during pregnancy in hypercalcemia condition. Data were analysed using ANOVA one-way analysis of variance followed by post hoc using Scheffe's test. Analysis was done using Statistical Pack-age for Social Sciences software (SPSS version 21).

3.0 RESULTS

Maternal hyperparathyroidism associated with hypercalcemia disorder resulted in adverse effects to foetal intrauterine growth developments. Foetal average BW, CRL, TBL, BPD FL and SCa showed significant reduction ($P < 0.05$) in maternal hypercalcemia compared to maternal with normal calcium level condition (Table 1).

3.1 Body Weight

Maternal HPT associated hypercalcemia produced a small to gestational age (SGA) litters with low body weight. Mean body weight were not significantly different between treatment and HPT groups except at 2nd gestation with 60 and 90 minutes ultrasound exposure ($P < 0.05$). Ultrasound intervention during 2nd gestational stage increases the progeny body weight in maternal HPT (Figure 2). However, mean body weight in treatment groups showed a significant difference in treatment group compared to control group at all stages (Figure 1). Thus, in relation to body weight, the outcome of ultrasound intervention is still considered small if compared to normal.

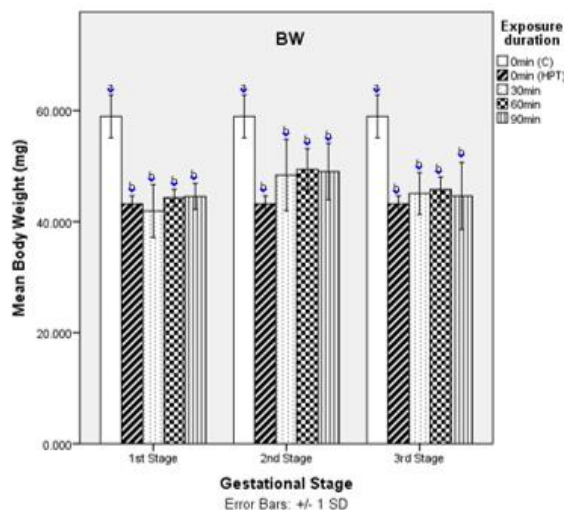


Figure 2 Introducing ultrasound during 2nd gestation show improvement in body weight

Scanning and Reconstruction using CTAn software (version 1.10.1.3 -Skyscan, Belgium)

3.2 Longitudinal Growth

Control progeny mean average CRL were significantly different between HPT and treatment groups (Figure 3.). Meanwhile, litters mean TBL were no significantly different between HPT and treatment groups except in 2nd gestational with 90 minute exposure duration. Comparing with control mean, TBL were significantly reduced in all treatment groups except in 1st gestation with 90 minutes ultrasound exposure, 2nd gestation and 3rd gestation with 30 and 60 minutes ultrasound exposure. Therefore, intervention during those stages and durations help to improve the length of foetal size in maternal HPT condition.

3.3 Biometric Parameter

Femoral length and Bi-parietal diameter are standard biometric parameters that are used to evaluate the development of the foetal. BPD in control groups showed no significant difference in treatment groups. Statistically significant BPD diameter increment in 2nd gestation with 60 and 90 minutes ultrasound exposure were identified compared to maternal HPT (Figure 3).

Femoral length in 1st gestational with 30 and 90 minutes ultrasound exposure and 3rd gestation with 60 and 90 minute ultrasound exposure showed a significant reduce in length compared to control group. While in 1st gestational stage with 60 minutes ultrasound exposure, 2nd gestation with 60 and 90 minute ultrasound exposure and 3rd gestation with 60 minutes ultrasound exposure showed a significant increment in femoral length compared to maternal HPT.

Table 1 Reference values for litters from control and maternal hyperparathyroidism

	Unit	No of Sample (n)	Control		Hyperparathyroidism	
			Mean (\bar{x})	SEM	Mean (\bar{x})	SEM
Maternal Ca	mmol/L	12	3.370	0.019	4.610	0.019
SCa	mmol/L	12	3.430	0.093	2.849	0.022
BW	mg	12	58.981	1.118	43.185	0.422
CRL	cm	12	10.250	0.917	9.375	0.103
TBL	cm	12	16.258	0.099	14.858	0.183
BPD	μm	12	16.293	0.227	15.449	0.059
FL	μm	12	18.872	0.293	16.604	0.207

a) Abbreviations: n, no. of sample; SEM, standard error; SCa, serum calcium level; BW, body weight; CRL, crown to rump length; TBL, total body length; BPD, biparietal diameter; FL, femoral

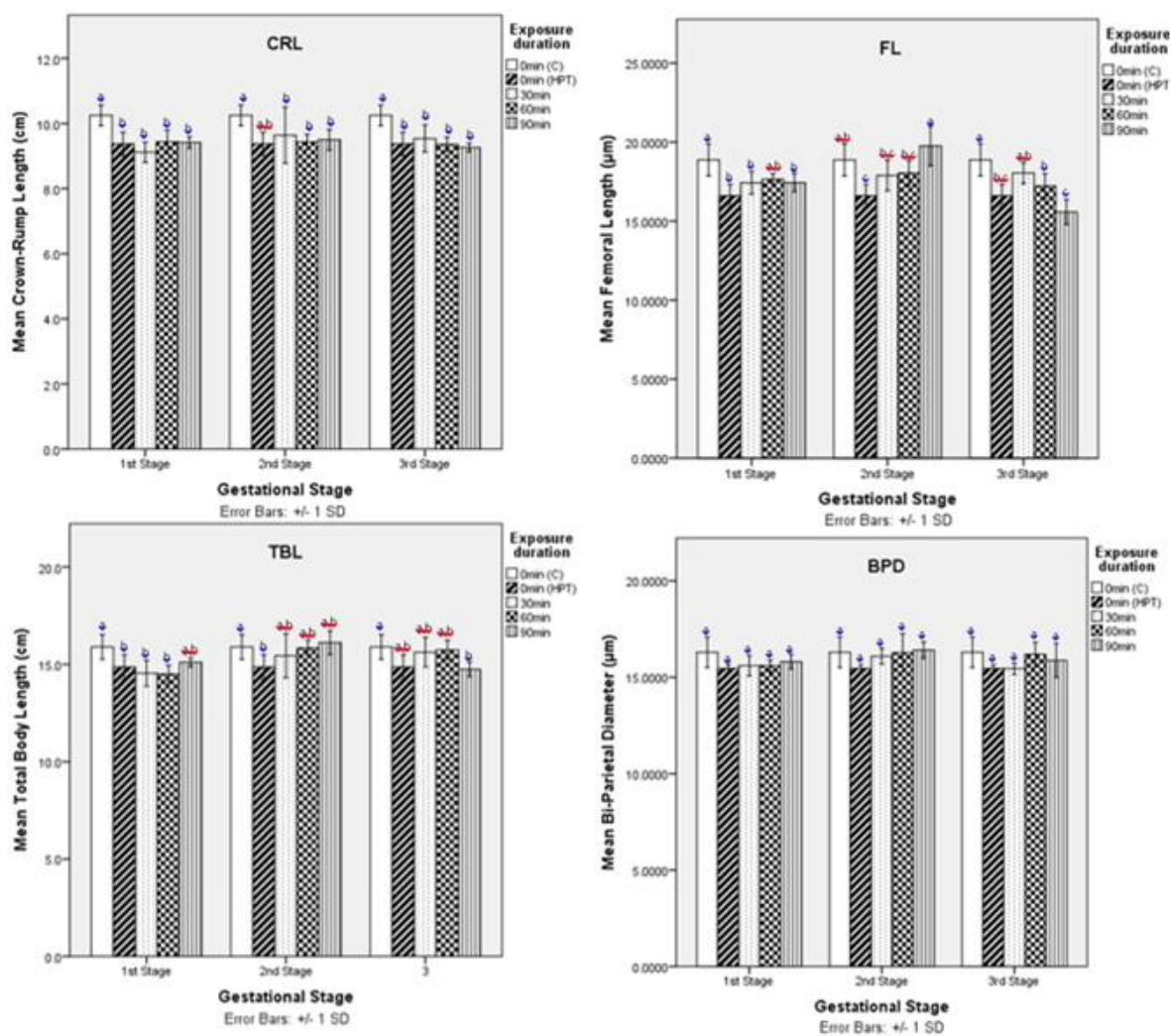


Figure 3 TBL in treatment groups yield a significant increase following ultrasound exposure. Increase in FL were noted in 2nd gestation and the BPD were also increase following ultrasound treatment

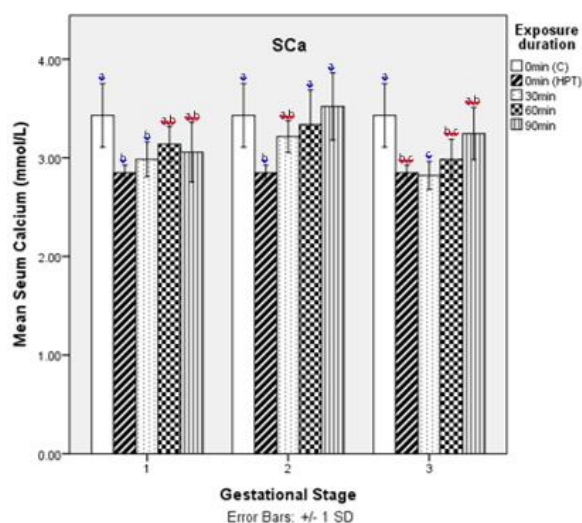


Figure 4 Significant increase in SCa were noted in 2nd gestation compare to maternal HPT

3.4 Serum Calcium Concentration

Serum calcium concentration in 1st gestational stage with 30 minutes ultrasound exposure and 3rd gestation with 30 and 60 minute ultrasound exposure show a significant low serum calcium concentration compared to control group. While serum calcium were significantly increased in treatment group from 2nd gestation stage (Figure 4.) and 3rd gestation stage with 90 minute ultrasound exposure compared to maternal HPT.

4.0 DISCUSSION

Birth weight is the strongest physiological indicator to predict the health of the foetal and direct effect over perinatal mortality [16]. It is known that maternal hypercalcemia produce SGA foetal with a 27% foetal body weight. The present result demonstrated that maternal HPT associated with hypercalcemia disorder produced hypocalcemia litter with significantly small sized and lower birth weight which is possibly caused by placenta malformation [17] due to the inadequate supply to support normal growth of the foetal. Nevertheless, a significant increment of body weight were detected after the ultrasound intervention during pregnancy in the middle of 2nd gestation with 60 and 90 minutes duration. Parathyroid ultrasound were given to the mother in order to reduce the parathyroid hormone level thus reducing serum calcium concentration in maternal hypercalcemia condition. mCalcium is the most abundant mineral in the human body and it is a vital mineral for newborn infant [18]. There exist a strong relationship between maternal serum calcium levels and neonatal calcium homeostasis [19]. Maternal parathyroid disorder associated with hypercalcemia suppressed the foetal parathyroid gland intrauterine

development [20] thus increasing the risk of hypocalcemia in postnatal life after abrupt disconnection between foetal and placenta. Following ultrasound treatment in middle of 2nd gestation with 30, 60 and 90 minutes and 3rd gestation with 90 minute duration, the foetal SCa concentration were significantly increased compared to hypocalcemia foetal in maternal HPT.

Normal development of foetal skeletal growth and mineralization requires sufficient mineral to be delivered from the placenta [21] Maternal hypercalcemia give birth to litter with lower body length which were possibly caused by disturbances in transplacental calcium flux[17]. The foetal TBL improved significantly when the ultrasound exposure was applied at the middle of 2nd gestation. BPD and femoral length is the biometric parameter that is used to evaluate the foetal development. Generally the femoral length registered an increase after the ultrasound exposure in maternal hypercalcemia.

Intrauterine growth retardation (UGR) is a major concern in modern obstetric [22]. In pathology it is defined as a decrease in normal growth resulting in small for gestation age (SGA) foetal. Maternal hypercalcemia resulted in foetal with symmetric SGA because the body weight, length and head diameter are significantly reduced [23, 24]. Prolonged disturbance that occur during the early stage of gestation will cause symmetric SGA [25]. Thus the heating effect from ultrasound exposure given at different gestational stage helps to reduce the PTH hormone level and revert the maternal calcium level to near normal concentration in hypercalcaemic condition. However, the physiological progeny outcome varies depending on the gestational sensitivity of the period development. Middle of 1st gestation stage is the embryonic stage, middle of 2nd gestational is the early foetal development or organogenesis phase while middle 3rd gestation is the end foetal development [26]. Present study demonstrated that ultrasound intervention given during middle 2nd gestational stage has resulted in a significant increase of the progeny mean average BW, CRL, TBL, BPD FL and SCa.

5.0 CONCLUSION

Hypercalcemia during pregnancy alters the foetal normal intrauterine growth and development which increased the risk of postpartum hypocalcemia complication. This ex-vivo study demonstrated the potential benefits of ultrasound local heating effect that might be of assistance in controlling PTH level in maternal hypercalcemia condition while foetus is still in the womb and therefore reducing the life – threatening post-natal complication in the early days of foetal life

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