The Relationship of Birth Weight, Body Shape and Body Composition at Birth to Altitude in Saudi Arabia

Relación de la Altitud con el Peso al Nacer, la Forma del Cuerpo y la Composición Corporal en Nacimientos en Arabia Saudita

Mohammed Elhabib Mohammed Khalid; Humeda Sweket Ahmed; Osama Mirghani Osman & Fahaid Hassan Al Hashem

SUMMARY: The objective of this work was to study the effect of high altitude on full term birth weight, body shape and body composition of newborn infants. Twenty five healthy pregnant Saudi women and their healthy newborns from high altitude (2850-3150 m) and equal numbers from low altitude (500 m). For each pregnant woman haemoglobin concentration, haematocrit value and blood pressures were measured and recorded immediately after admission to hospital for delivery. Fetal haemoglobin concentration and haematocrit value were determined immediately after delivery. Determination of the newborn's body shape and composition were made from anthropometric measurements which were performed two hours after delivery. Placental weight was determined immediately after its delivery. Placentae were then examined histologically. Compared with their respectives from lowland, the pregnant women from high altitude and their placentae showed haemotogical and histological changes suggestive of maternal and placental hypoxia respectively. There was no haematological evidence suggesting that the high altitude fetuses experienced a greater degree of hypoxia in utero than did the low altitude fetuses. Compared with lowland newborns highland newborns were significantly lighter but fatter and have significantly greater head circumference: birth weight ratios and abdominal circumferences. These differences in body physique between high and lowland neoborns appeared to be mainly secondary to placental hypoxia resulting from maternal hypoxia which in turn was caused by high altitude hypoxia. The altered body physique at birth due to high altitude hypoxia appeared to be not mediated by fetal hypoxia, but possibly by other mechanisms induced by placental hypoxia.

KEY WORDS: High altitude; Birth weight; Body shape; Body composition.

INTRODUCTION

Low baby weight at birth is a risk factor for many diseases in adulthood including cardiovascular diseases (Rich-Edwards *et al*.,1997) type 2 diabetes (Frayling & Hattersley, 2001), liver disease (Donma & Donma, 2003), stroke (Martyn *et al*., 1996) and metabolic syndrome (Visentin *et al*., 2014). However, other studies have shown that newborns with disproportionate or asymmetric growth retardation resulting from alteration in body composition during pregnancy are more prone to diseases in adulthood than newborns with symmetrical small body weight (Dashe *et al*., 2000). Hypobaric hypoxia resulting from high altitude has been recognized as one of the principle causative factor of small baby size at birth (Julian *et al*., 2008). Also the incidence of diseases associated with foetal growth restriction such as pre-eclampsia is higher at high altitude than at low altitude (Keyes *et al*., 2003). The decline in birth weight

with increasing altitude is reconfirmed in the southwestern heights of the Kingdom of Saudi Arabia (Khalid *et al*., 1997). However, no attempt has been made to describe the body shape and determine the body composition of newborns at high altitude areas of southwestern Saudi Arabia (2850-3100 m) where both environmental factors and population genotypes differ from other studied areas. The present study was, therefore, undertaken to:

a-Describe the body shape and determine the body composition of newborn infants at high altitude and compare them with their counterparts born at low altitude.

b- Determine any possible relationship of the indices of body shape and body composition at birth to maternal haemoglobin concentrations and haematocrit values at the

Department of Physiology, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia.

end of gestation, placental morphology (placental weight, incidences of syncytial knots and cytotrophoblastic cells and foetal capillary numbers) and fetal haemoglobin concentrations and haematocrit values at birth.

Changes in maternal haemoglobin concentration and haematocrit value at the end of gestation, placental morphology and foetal haemoglobin concentration and haemotocrit value at birth were used as indicators for the degree of maternal, placental and fetal hypoxia respectively.

MATERIAL AND METHOD

This study was carried out at high and low altitude areas of Aseer province in the Southwestern part of the Kingdom of Saudi Arabia. At high altitude, Abha City (altitude 3000,barometric pressure 550 mmHg) was selected for the study. For comparison, Mohayel City at low altitude (altitude 500 m, barometric pressure 720 mmHg) was selected. The permanent residents in the two cities are racially homogenous. All are Arabs and Saudi nationals. Meat, chicken and rice constitute the major dietary items for residents in the two cities. Primary health care in Aseer province is provided through a widespread network of 208 primary health care centres (PHC). Each centre has a well-defined catchment area and population. Secondary and tertiary care services in the province are provided through a network of 15 hospitals.

Subjects were recruited from pregnant women who attended Abha Maternity Hospital and Mohayel General Hospital for delivery. The inclusion criteria for the study included pregnant Saudi women aged 18-35 years, gravida two to gravida four, with known gestational age by dates and/or ultrasound, born and in permanent residence in the designated study areas. The exclusion criteria were any disease during pregnancy, bleeding in pregnancy, multiple pregnancies, poor antenatal attendance, smokers, perinatal or postnatal detection of congenital malformations and post-term pregnancies or any discrepancy in gestational age between dates and ultrasound. The subjects who satisfied the above mentioned criteria were twenty five pregnant women from Abha City and an equal number from Mohayel City. Immediately after admission to hospital for delivery, the blood pressures for each subject at high and low altitudes were measured in a lying position by a well trained nurse using mercury sphygmomanometer. Three readings at 5 minutes intervals were taken and the mean was recorded. Diastolic blood pressure was taken at Kortkoff phase V. A venous blood sample was then taken for determination of haemoglobin concentration and haematocrit value using

Colter (J.T.). Immediately after normal spontaneous vaginal delivery of any baby in the two groups a cord blood sample was taken for determination of haemoglobin concentration and haematocrit value using Colter (J.T.). For each newborn in the two groups anthropometric measurements including weight, length, body circumferences and skinfold thicknesses were performed using standard methods and at standard sites (Jelliffe, 1966) two hours after delivery. The equipments used were of well-tested design and calibrated at frequent intervals. Body weight was measured and recorded to the nearest 0.01 Kg using an infant's beam balance. All newborns were weighed naked. Crown–heel length was measured using an infant's board with the infant lying flat and legs extended and recorded to the nearest 0.1 cm. All circumferences were measured using an inelastic tape and recorded to the nearest 0.1 cm. The greatest head circumference was measured by placing the tape firmly around the frontal bones, just superior to the supra-orbital ridges, passed around the head at the same level on each side and laid over the maximum occipital prominence at the back. Waist circumference was measured at the mid-point between the bottom of the rib cage and above the top of the iliac crest with the tape placed perpendicular to the mid-axillary line in mid inspiration. All skinfold thicknesses were measured with Harpenden skinfold caliper on the right side of the body and recorded to nearest 0.1 mm. The skinfold over the biceps muscle was taken upon the front of the arm midway between the acromion process of the right scapula and the olecranon process of the right ulna. Triceps skinfold was taken up at the back of the arm also midway between the acromion process of the right scapula and the olecranon process of the right ulna. Subscapular skinfold was taken up just below and lateral to the angle of the right scapula and suprailiac skinfold was taken up just above the right iliac crest. Head circumference: Birth weight ratios were computed from head circumference (cm) and birth weight (kg).

Estimates of fat mass (FM) were made from the skinfold measurements using the equation derived by Schmelzle & Fusch (2002):

Fat mass (FM) in grams = $68.2 \cdot \Sigma SFT^{0.0162 \cdot L} - 172.8$

Where:

Σ SFT = Sum of the 4 skinfold measurements (mm), L = Crown–heel length (cm).

The total body fat expressed as percentage of body weight (percentage of fat) and the total body fat free mass expressed as percentage of body weight (percentage of fat free mass) were then calculated. The following equations were used:

1110

Percentage of fat = $\dfrac{(FM\ (Kg)}{Birth\ weight\ (Kg))}$ X100

Percentage of fat free mass = 100 - percentage of fat

Immediately after the delivery of each placenta, placental weight was measured using Sartorius precision balance and recorded to the nearest 0.5 g. Placentae were then fixed in 10 % buffered formalin solution. Samples for histology were taken from the periphery and centre using a transect sampling line which always passes through the cord insertion point (Junaid *et al.*, 2014). All samples were washed in phosphate buffer saline (PBS) and fixed overnight in neutral buffered formalin. Fixed samples were then dissected into 10-15 small pieces which were merged randomly in a cassette prior to wax embedding to ensure physical randomization of the tissue architecture as described by Stringer *et al.* (1982). Five mm wide sections from each block of randomly orientated, were cut from each slice and stained by Hematoxylin and Eosin (H&E) for identification of cytotrophoblastic cells and syncytial knots, respectively. Cytotrophoblastic cells and syncytial knots were counted in 40 terminal villi from 40 different, but randomly selected, fields in each section stained by H&E. Histological identification of syncytial knots and the cytotrophoblastic cells was done according to Fox (1964). The number of villi with cytotrophoblastic cells and syncytial knots were recorded and the results expressed as percentage of total. The fetal capillaries were counted in 40 terminal villi from 40 different, but randomly selected, fields in each section stained by H&E and expressed as number.

Statistical Analysis. The collected data were compiled and fed into IBM computer. SPSS version 20 (IBM Corp., Armonk, N. Y.) was used for standard statistical analysis. Descriptive data are presented as mean +/- standard deviations or percentages. The student T-test and Z-/ test were used to compare between two means and two percentages respectively. Spearman's correlation coefficient was used to test for association between two variables. P values < 0.05 were considered significant.

RESULTS

This study was confined to young pregnant women ranging in age from 18-35 years and their newborns. Table I shows the clinical data pertaining to the pregnancies at high and low altitudes. There were no significant differences in the mean maternal age and gestational age between high and lowland pregnant women. The mean haemoglobin concentration, haematocrit value, systolic and diastolic blood pressures were significantly higher at high altitude than low altitude. The mean fetal haemoglobin concentration and haematocrit value were nearly the same in infants born at high altitude (16.0±1.9gm / dl and 53.1±6.5 % respectively) as in infants born at low altitude (15.9±1.5 gm/dl and 52.6±4.9 % respectively). (P < 0.9 for both).Table II demonstrates the physical characteristics and body composition of babies born at high and low altitudes. Babies born at high altitude were found to be significantly lighter and slightly but insignificantly shorter than their counterparts born at low altitude (P<0.04 and <0.07 respectively). The mean head and waist circumferences were significantly greater at high altitude than at low altitude (P <0.001 and < 0.002 respectively). No significant differences in biceps skinfold thickness was noticed between babies born at high and low altitudes. The mean triceps, subscapular and suprailiac skinfold thicknesses were significantly greater at high altitude than at low altitude (P <0.01, <0.001 and <0.001 respectively). The head circumference (cm): birth weight (kg) ratio was significantly greater at high altitude than at low altitude (P<0.001). The body fat expressed as percentage of body weight (percentage of fat) was significantly greater among highland newborn babies than lowland newborn babies. When the percentage of fat free mass was considered, opposite trend was noticed between high and lowland newborn babies.

A summary of the macro and microscopic findings seen in placentae are presented in Figure 1. Placental weight, although greater at high altitude compared to low altitude,

Table I. Mean values and standard deviations of the means (SD) of the clinical data pertaining to pregnancies at high and low altitudes.

	High altitude (n=25)		Low altitude (n=25)		P value
	Mean	SD	Mean	SD	
Maternal age (years)	26.0	4.0	25.4	3.5	NS
Number of deliveries	3.0	0.75	2.8	0.74	NS
Gestational age (weeks)	39.2	0.9	39.1	1.2	NS
Haemoglobin concentration (g/dl)	12.3	1.2	10.8	1.6	<0.01
Haematocrit (%)	41.0	4.3	36.8	6.3	<0.001
Systolic blood pressure(mmHg)	117.9	10.1	100	6.5	<0.001
Diastolic blood pressure(mmHg)	68.8	5.4	66.0	3.8	<0.04

NS - Not significant

Table II. Mean Values and standard deviations of the means (SD) of body measurements and composition of newborn babies at high and low altitudes.

	High altitude (n=25)		Low altitude (n=25)		P value
	Mean	SD	Mean	SD	
Birth weight (Kg)	2.9	0.3	3.1	0.4	< 0.04
Birth length (cm)	49.1	1.7	50.4	3.2	NS
Head circumference (cm)	34.5	1.0	32.9	1.6	< 0.001
Waist circumference (cm)	30.3	1.3	28.6	2.2	<0.002
Biceps skin fold (mm)	4.4	0.8	4.2	1.2	NS
Triceps skin fold (mm)	4.6	0.8	3.9	0.9	<0.01
Subscapular skin fold (mm)	4.5	0.6	3.8	0.9	<0.001
Suprailiac skin fold (mm)	4.6	0.8	3.4	0.8	<0.001
Head circumference : birth weight ratio(cm:kg)	11.9	0.012	10.6	0.16	<0.001
Percentage of fat (%)	18.3	2.9	14.3	3.5	<0.001
Percentage of free fat mass (%)	81.7	2.9	85.7	3.5	< 0.001

NS - Not significant.

the difference was not statistically significant. Histological examination revealed that the incidences of villi with syncytial knots and that of cytotrophoblastic cells were significantly greater at high altitude compared to low altitude. In addition, there was a significant rise in the number of capillary lumina at high altitude compared to low altitude. Figure I shows photomicrographs of H & E stained placental tissues from high and low altitude.

At both high and low altitudes maternal haemoglobin, haematocrit, systolic and diastolic blood pressures on one hand showed positive but insignificant associations with placental weight and positive significant correlations with incidences of syncytial knots and cytotrophoblastic cells and number of capillary lumina on the other hand (Table III) (maternal haemoglobin and haematocrit were used as indicators for maternal hypoxia and placental weight and incidences of syncytial

Table III: Intercorrelations between maternal haemoglobin, haematocrit, blood pressures and placental weight, incidences of syncytial knots, cystotrophoblastic cells, number of foetal capillaries.

	Placental weight	Incidence of Syncytial	Incidence of	No of capillaries
	r	r	r	r
Maternal haemoglobin	+0.11 (NS)	+ 0.42**	+0.43**	0.39**
Maternal haematocrit	+0.10 (NS)	+0.33*	+ 0.35*	0.29*
Systolic blood pressure	+0.04 (NS)	+0.73**	+0.73**	0.67*
Diastolic blood pressure	+0.23 (NS)	+0.30*	+ 0.31*	+0.30*

r = Spearman's correlation coefficient, *: P<0.05, **:P<0.01, NS :Not significant.
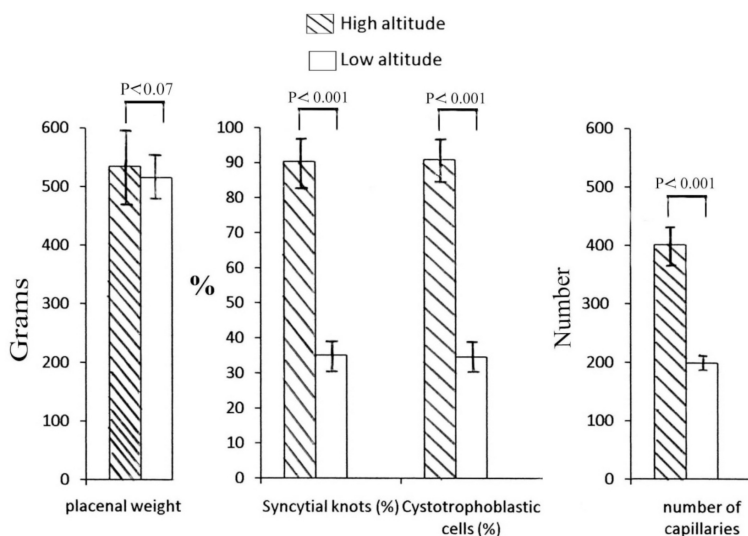

Fig. 1. A summary of the macro and microscopic findings in placentae (mean ± standard deviation).

knots and cytotrophoblastic cells and fetal capillary number were used as indicators for placental hypoxia). Placental weight did not show any significant associations with birth weight indices of foetal body shape (length, head circumference: birth weight ratio and abdominal circumference) or indices of body composition (percentage of body fat and percentage of fat free mass) while the incidences of syncytial knots and that of cytotrophoblastic cells and the number of capillary lumina on one hand showed negative and significant correlations with birth weight, birth length percentage of fat free mass and positive significant association with head circumference: birth weight ratio, abdominal circumference and percentage of fat on the other hand (Table IV).

No significant associations existed between fetal haemoglobin and haematocrit on one hand and birth weight, indices of fetal body shape and indices of body composition on the other hand (Not shown on the table).

Table IV. Intercorrelation between birth weight, birth shape indices, body composition indices adverse and placental weight, incidences of syncytial knots, cytotrophoblastic cells, number of foetal capillaries.

	Incidence of Syncytial knots	Incidence of cystotrophoblasts	No of capillaries
	r	r	r
Birth weight (kg)	-0.33*	-0.33*	- 0.34*
Birth length (cm)	-0.32*	-0.31*	-0.32*
Head circumference	+0.46**	+0.46**	+0.42**
Waist circumference (cm)			
Head circumference/Birth weight (cm/kg)	+ 0.38**	+ 0.38**	+ 0.31*
Percentage of fat (%)	+0.56**	+0.56**	+0.56
Percentage of fat free mass	+0.48**	+0.47**	+0.46**
	-0.47**	-0.48**	-0.46**

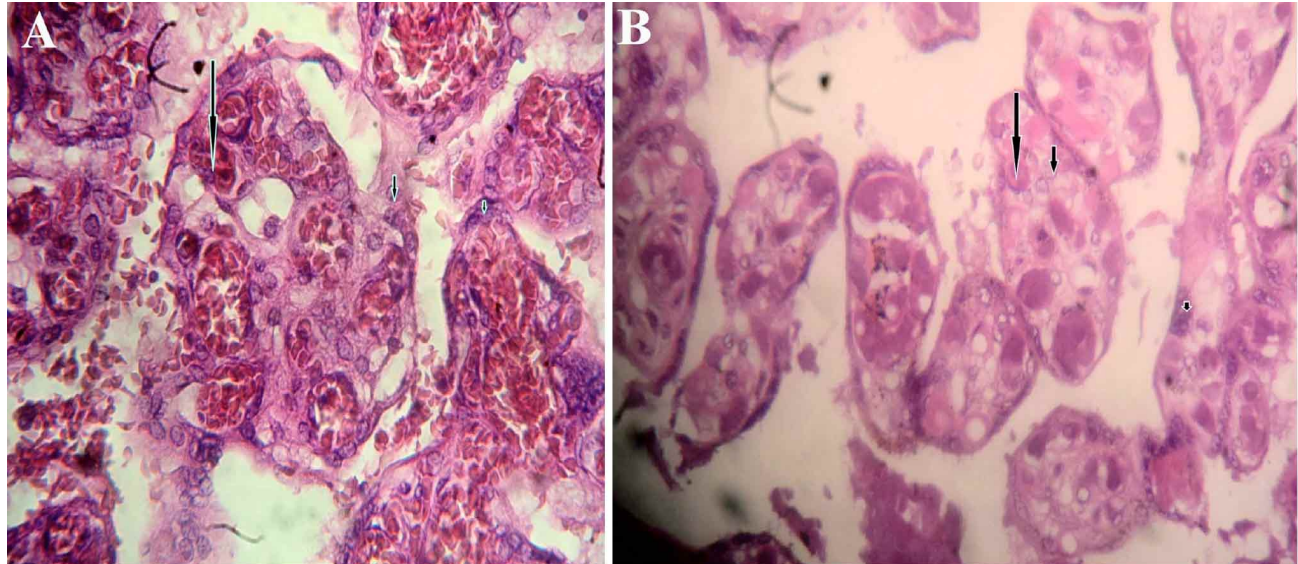r = Spearman's correlation coefficient, *: P<0.05, **:P<0.01, NS :Not significant.

Fig. 2. Photomicrograph of placental tissue from high altitude (A) and low altitude (B) with syncytial knots (arrowheads), cytotrophoblastic cells (small arrows) and foetal capillaries (big arrows). H&E -stained sections.

DISCUSSION

In this study babies born at high altitude were found to be significantly lighter but relatively fatter when compared with their counterparts born at low altitude. The reduced birth weight reported for high altitude babies is in agreement with previous published work on the same population (Khalid *et al*.) and appeared to be altitude dependent rather than due to differences in other factors acting to reduce birth weight, such as maternal health, age, socioeconomic

conditions, parity, gestational age, pregravid and gravid BMI, smoking, pre-natal care visits and female newborn- since such factors did not differ between the two altitudes (see method) or did not relate to reduction in birth weight (Jensen & Moore 1997).

The mechanism by which high altitude hypoxia causes decrease in birth weight is not exactly known. However, it has been suggested by earlier investigators to be due to direct effect of a reduced oxygen tension on fetal mitotic rate (Malaspina *et al.*, 1971). However, recently Zamudio *et al.* (2010) argued that the reduction in fetal growth due to high altitude hypoxia is mediated not by limitation on oxygen availability but foetal hypoglycemia. More recently Yung *et al.* (2012) suggested that the reduced uterine artery blood flow which occurs during high altitude hypoxia may invoke the involvement of intervening factors, such as ischaemia/ perfusion injury and/or oxidative stress which stimulate the unfolded protein response and actively decrease fetal growth.

Fetal growth is regulated mainly by the delivery of oxygen and nutrients mainly glucose to the foetus via maternal uteroplacental circulation. In this study, we did not find any indication that the high altitude foetus experienced a greater degree of hypoxia in utero than does the low altitude fetus. The mean fetal heamoglobin concentration and haematocrit value at birth were nearly the same in low and high altitude newborns. Therefore reduced birth weight reported for Saudi high altitude babies appeared to be not mediated by fetal hypoxia, but possibly by other mechanisms induced by placental hypoxia. Whatever mechanism involved the end result appeared to be reduction in the overall energy production by the high altitude foetesus compared to low altitude ones. Under these adverse intrauterine environments, the high altitude fetus appeared to maximize its survival chance by diverting the energy to vital organs such as the brain (Godfrey & Barker, 2001) and channeling substrate away from relatively less vital organs such as skeletal muscles and viscera. The former was evident by the increase in the head circumference: birth weight ratio and the latter by the decrease in fat free mass among Saudi high land neoborns compared to lowland newborns. This type of asymmetric growth retardation has been reported before Giussani *et al.* (2001) and was found to be associated with stroke in adulthood (Martyn *et al.*). This may be taken to indicate that Saudi babies born at high altitude are more susceptible to stroke in adulthood than their counterparts born at low altitude.

Our finding of relative fatness among Saudi high altitude newborns compared to low altitude ones is particularly striking in view of their low birth weight and shorter length. However, it is consistent with previous reports

from other parts of the world (Ballew & Haas 1986), but inconsistent with other investigators who reported either reduced fatness at high altitude (Galan *et al.*, 2001) or no significant difference (Schwartz *et al.*, 2013). The discrepancies may be the result of variation in altitudinal levels and ethnicity of the mother as well as technical problems associated with indirect methods that have been used to evaluate body fat in newborns. Furthermore, most if not all of the investigators in the field used either skinfold measurements or fetal biometry to assess only subcutaneous fat and did not consider deeper fat deposits which could relate differently to birth weight. In this study all the percentage of fat was found to be significantly greater at high altitude than at low altitude. It follows, therefore, that the low birth weight measured in Saudi newborn infants at high altitude resulted mainly from reduced percentage of fat free mass which was found to be significantly lower at high altitude compared to low altitude.

The increased fatness and decreased fat free mass among high altitude newborns compared to low altitude infants, observed in this study, appeared to be secondary to placental hypoxia resulting from maternal hypoxia which in turn was caused by high altitude hypoxia. There is positive and significant relationship between the indices for maternal hypoxia on one hand and placental hypoxia on the other hand. In turn, there is positive and significant association between placental hypoxia and percentage of fat and negative and significant correlations with percentage of fat free mass. Fat accretion occurs primarily in the last trimester of gestation (Herrera & Amusquivar, 2000). It is quite possible, therefore, during this period of gestation the Saudi high land newborn diverted energy for more fat accretion to safeguard against extrauterine hypothermia and hypoglycemia which are known to occur in newborns with low birth weight (McIntire *et al.*, 1999).

In conclusion, the determination of body shape and body composition at birth, in this study, revealed that the smallness of Saudi high altitude newborn infants compared to their counterparts born at low altitude was not proportional. The high altitude newborns were on average 200 g smaller and 1.3 cm shorter, have higher head circumference: birth weight ratio, greater abdominal circumference, and lower fat free mass and higher fat mass. Therefore, in effect, they are born obese if obesity is to be defined as excess of body fat. However, the excess body fat deposited during the late intrauterine life might persists and become manifest as adiposity increase during childhood.

A limitation to this study is that the equation used for estimation of total body fat was derived from study on white infants. However, the equation was used for both high and

low altitude groups to test for relative fatness and not for accurate estimation of body fat. It appears that there is a need for local studies - using imaging techniques - among Saudi newborn infants to enable the derivation of valid regression equations for the calculation of body fat from skinfold thickness measurements.

ACKNOWLEDGEMENTS

MOHAMMED E.M. KHALID, HUMEDA S. AHMED, OSAMA M. OSMAN, FAHAID HASSAN AL HASHEM. Relación de la altitud con el peso al nacer, la forma del cuerpo y la composición corporal en nacimientos en Arabia Saudita. *Int. J. Morphol., 34(3)*:1109-1116, 2016.

El objetivo de este trabajo fue estudiar el efecto de altura elevada en el peso al nacer a término, la forma del cuerpo y la composición corporal de los recién nacidos. Se estudiaron veinticinco mujeres saudíes, embarazadas sanas y sus recién nacidos sanos, de una zona de gran altura (2850 - 3150 m) y un número igual de una zona de baja altitud (500 m). Las concentraciones de hemoglobina y los valores de hematocrito de las mujeres embarazadas fueron medidas y registradas inmediatamente después de la admisión al hospital para el parto. La concentración de hemoglobina fetal y el valor del hematocrito se determinaron inmediatamente después del parto. Las determinaciones de la forma y composición del cuerpo del recién nacido se realizaron a partir de mediciones antropométricas dos horas después del parto. El peso de la placenta se determinó inmediatamente después de su expulsión. Las placentas fueron examinadas histológicamente. En comparación con sus pares de áreas de baja altura, las mujeres embarazadas de gran altura y su placenta mostraron cambios hematolológicos e histológicos indicativos de hipoxia materna y placentaria, respectivamente. No hubo evidencia hematológica lo que sugiere que los fetos de zonas de gran altura experimentaron un mayor grado de hipoxia en el útero, que los fetos de baja altura. En comparación con los recién nacidos de las tierras bajas de la montaña, los recién nacidos fueron significativamente más livianos pero más obesos, y se registrará la circunferencia de la cabeza: se relacionó el peso al nacer y la circunferencia abdominal. Estas diferencias en la constitución corporal entre neonatos de alturas elevadas y bajas parecían ser principalmente secundarias a la hipoxia placentaria, en consecuencia de la hipoxia materna, que a su vez fue causada por la hipoxia de la altura. La composición corporal alterada del recién nacido por hipoxia de altura, parecía no estar mediado por la hipoxia fetal, por el contrario estarían producidos posiblemente por otros mecanismos inducidos por la hipoxia placentaria.

PALABRAS CLAVE: Gran altura; Peso al nacer; Forma del cuerpo; Composición corporal.

REFERENCES

Ballew, C. & Haas, J. D. Altitude differences in body composition among Bolivian newborns. *Hum. Biol., 58(6)*:871-82, 1986.

Dashe, J. S.; McIntire, D. D.; Lucas, M. J. & Leveno, K. J. Effects of symmetric and asymmetric fetal growth on pregnancy outcomes. *Obstet. Gynecol., 96(3)*:321-7, 2000.

Donma, M. M. & Donma, O. Low birth weight: a possible risk factor also for liver diseases in adult life? *Med. Hypotheses, 61(4)*:435-8, 2003.

Fox, H. The villous cytotrophoblast as an index of placental ischaemia. *J. Obstet. Gynaecol. Br. Commonw., 71*:885-93, 1964.

Frayling, T. M. & Hattersley, A. T. The role of genetic susceptibility in the association of low birth weight with type 2 diabetes. *Br. Med. Bull., 60(1)*:89-101, 2001.

Galan, H. L.; Rigano, S.; Radaelli, T.; Cetin, I.; Bozzo, M.; Chyu, J.; Hobbins, J. C. & Ferrazzi, E. Reduction of subcutaneous mass, but not lean mass, in normal fetuses in Denver, Colorado. *Am. J. Obstet. Gynecol., 185(4)*:839-44, 2001.

Giussani, D. A.; Phillips, P. S.; Anstee, S. & Barker, D. J. Effects of altitude versus economic status on birth weight and body shape at birth. *Pediatr. Res., 49(4)*:490-4, 2001.

Godfrey, K. M. & Barker, D. J. Fetal programming and adult health. *Public Health Nutr., 4(2B)*:611-24, 2001.

Herrera, E. & Amusquivar, E. Lipid metabolism in the fetus and the newborn. *Diabetes, Metab. Res. Rev., 16(3)*:202-10, 2000.

Jelliffe, D. B. The assessment of the nutritional status of the community (with special reference to field surveys in developing regions of the world). *Monogr. Ser. World Health Organ., 53*:3-271, 1966.

Jensen, G. M. & Moore, L. G. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am. J. Public Health, 87(6)*:1003-7, 1997.

Julian, C. G.; Galan, H. L.; Wilson, M. J.; DeSilva, W.; Cioffi-Ragan, D.; Schwartz, J. & Moore, L. G. Lower uterine artery blood flow and higher endothelin relative to nitric oxide

metabolite levels are associated with reductions in birth weight at high altitude. *Am. J. Physiol. Regul. Integr. Comp. Physiol., 295(3)*:R906-15, 2008.

Junaid, T. O.; Brownbill, P.; Chalmers, N.; Johnstone, E. D. & Aplin, J. D. Fetoplacental vascular alterations associated with fetal growth restriction. *Placenta, 35(10)*:808-15, 2014.

Keyes, L. E.; Armaza, J. F.; Niermeyer, S.; Vargas, E.; Young, D. A. & Moore, L. G. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. *Pediatr. Res., 54(1)*:20-5, 2003.

Khalid, M. E.; Ali, M. E. & Ali, K. Z. Full-term birth weight and placental morphology at high and low altitude. *Int. J. Gynaecol. Obstet., 57(3)*:259-65, 1997.

Malaspina, L.; Quilici, J. C. & Ergueta Collao, J. Modificaciones de las condiciones del cultivo celular en la altura. *Ann. Inst. Boliv. Biol. Altura, 2*:3-5, 1971.

Martyn, C. N.; Barker, D. J. & Osmond, C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet, 348(9037)*:1264-8, 1996.

McIntire, D. D.; Bloom, S. L.; Casey, B. M. & Leveno, K. J. Birth weight in relation to morbidity and mortality among newborn infants. *N. Engl. J. Med., 340(16)*:1234-8, 1999.

Rich-Edwards, J. W.; Stampfer, M. J.; Manson, J. E.; Rosner, B.; Hankinson, S. E.; Colditz, G. A.; Willet, W. C. & Hennekens, C. H. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *B. M. J., 315(7105)*:396-400, 1997.

Schmelzle, H. R. & Fusch, C. Body fat in neonates and young infants: validation of skinfold thickness versus dual-energy X-ray absorptiometry. *Am. J. Clin. Nutr., 76(5)*:1096-100, 2002.

Schwartz, J.; Cioffi-Ragan, D.; Wilson, M. J.; Julian, C. G.; Beatty, B.; Moore, L. G. & Galan, H. L. Little effect of gestation at 3,100 m on fetal fat accretion or the fetal circulation. *Am. J. Hum. Biol., 25(4)*:544-9, 2013.

Stringer, B. M.; Wynford-Thomas, D. & Williams, E. D. Physical randomization of tissue architecture: an alternative to systemic sampling. *J. Microsc., 126(Pt. 2)*:179-82, 1982.

Visentin, S.; Grumolato, F.; Nardelli, G. B.; Di Camillo, B.; Grisan, E. & Cosmi, E. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis, 237(2)*:391-9, 2014.

Yung, H. W.; Cox, M.; Tissot van Patot, M. & Burton, G. J. Evidence of endoplasmic reticulum stress and protein synthesis inhibition in the placenta of non-native women at high altitude. *F. A. S. E. B. J., 26(5)*:1970-81, 2012.

Zamudio, S.; Torricos, T.; Fik, E.; Oyala, M.; Echalar, L.; Pullockaran, J.; Tutino, E.; Martin, B.; Belliappa, S.; Balanza, E. & Illsley, N. P. Hypoglycemia and the origin of hypoxia-induced reduction in human fetal growth. *PLoS One, 5(1)*:e8551, 2010.

Corresponding author:
Prof. Mohammed Elhabib Mohammed Khalid
Department of Physiology
College of Medicine
King Khalid University
P.O.Box 641
SAUDI ARABIA

Mobile phone No.:00966507333546

Email:mhkhalid999@yahoo.com