Maternal and paternal influence on early intrauterine foetal size and birth size in girls and boys

Med-3950
5. årsoppgave

Profesjonsstudiet i medisin ved Universitetet i Tromsø

Student:
Lise Hansen Skåren
MK-08

Veileder:
Åshild Marit Bjørnerem
Overlege, Kvinneklinikken, Universitetssykehuset Nord- Norge, Tromsø

Tromsø

Vår 2013

CONTENTS

Acknowledgements

I especially want to thank my supervisor, Dr Åshild Bjørnerem, for all of her comments, intellectual direction and great patience during my work on this thesis. Further I want to thank her for introducing me to the field of gynaecology, which was of great inspiration with lots of fun. I also wish to thank Professor Ego Seeman, Associate Professor Susan P Walker and the research team in Australia for access to the data that is collected at the University in Melbourne, Australia, and all participants who made the study possible. I am very grateful that Norsk Gynekologisk Forening (NGF) gave me the opportunity to present our result at the annual meeting in Tromsø in October 2012; it was a really great experience for me.

Abstract

Background: Low birth weight is associated with diseases later in life. The mechanisms for these associations are not well known. Achieving a better understanding of the determinants for intrauterine growth, may contribute to optimize health in adulthood. If the hypothesis concerning "Maternal Constraint" is correct for humans as shown in animal experiments, we expect the maternal size, but not the paternal size, to influence on growth before birth, and size of both parents to influence on growth after birth. We aimed to study the effect of parental size on foetal size and birth size and whether these effects were different for boys and girls.

Methods: A total of 400 healthy pregnant women 20-42 years of age were recruited at The Mercy Hospital for Woman, Melbourne, Australia, during 2008-2009. Foetal femur length was measured using ultrasound in 20 and 30 weeks gestation. Weight and height were measured in both parents, and in their offspring at birth. The effect of maternal and paternal size on foetal size and birth size is examined in linear regression analysis.

Results: Foetal femur length early and late in gestation was associated with maternal weight (standardized coefficient (STB) 0.14 and 0.22, both $p < 0.01$), not height, with no effect of paternal size. Birth weight was associated with maternal height in both sexes independent of maternal weight and paternal size. In girls, the paternal height predicted birth length (STB 0.29, $p < 0.01$) with no independent effect of maternal size. In boys, the maternal height predicted birth length (STB 0.30, $p < 0.01$) with no independent effect of paternal size.

Conclusion: Early foetal growth was determined by maternal proportions, with no effect of paternal proportions. There seems to be a sex-difference, where maternal height predicts birth length in boys, and paternal height predicts birth length in girls.

Introduction

Low birth weight and relative thinness at birth is associated with increased risk for diseases later in life, such as osteoporosis, diabetes mellitus and cardiovascular disease (1-4). Variance in foetal dimensions has a large genetic component but environmental factors also contribute to this variance (5). The mechanisms for these associations are not well known, but understanding the determinants of pattern of intrauterine growth may contribute to optimize health in adulthood.

Maternal constraint is considered as an important factor for determining foetal growth and more strongly in young mothers, small mothers, nulliparous and multiple pregnancies (6-9). This concept is poorly understood, but it is possible that it is about genetic and epigenetic maternal factors expressed in placenta that limit foetal growth (7). Maternal constraint is an important physiological mechanism for the mother’s own survival and ability to give birth to her offspring, but not without long-term consequences (8). There is increasing evidence that maternal constraint; with poor foetal growth, may involve a risk of disease in adult life (1-4).

There is no doubt that maternal proportions are an important determinant for birth weight in the offspring. The paternal role has been less discussed in this context and to the best of our knowledge there is no data on the father’s influence on foetal size or intrauterine growth. However, we know from earlier studies that paternal proportions affect the offspring’s birth weight (10-12). Previous studies have reported that maternal weight has a greater impact than paternal weight on offspring birth weight (11). Griffith et al. suggested that the paternal genetic factors affect birth weight independently of maternal influence. Morrison et al. reported that paternal height had a significant effect, while paternal BMI had no effect on birth weight (13). They demonstrated the effect of maternal constraint by showing that father’s height had less effect on birth weight if mother was shorter. As far as we know there are no earlier reports that have studied the paternal size effect on birth length. The aim of this project was to study the effect of maternal and paternal height and weight on foetal femur length early and late in gestation, birth length and weight, and whether there was any difference between sexes. We hypothesized that foetal and neonatal size correlates more strongly with maternal than paternal height and weight, due to maternal constraint.

Methods

Between July 2008 and June 2009, 400 healthy pregnant women aged 20-42 years with a normal single foetus were recruited at their 20-week routine ultrasound scan at The Mercy Hospital for Women in Melbourne, Australia. Among them, 356 women were willing to have an additional ultrasound scan at 30 week, and 345 of their partners were willing to participate. After birth 326 new-borns, born at term, were available for measurements.

All participants gave written informed consent. Mercy Health & Aged Care Human Research Ethics Committee approved the study. Gestation was determined based on the last menstrual period unless the gestation assessed by the first ultrasound measurements (CRL before 12 weeks, biparietal diameter at 12-20 weeks) differed by more than 7 days; gestation was then based on assessment by ultrasound. We excluded foetuses that had major malformation detected by ultrasound scan or a preterm delivery before 37 weeks gestation.

A questionnaire addressing maternal life style factors such as smoking and alcohol use, were assessed. Foetal growth was monitored using 2D ultrasound of femur length (FL) at 2 occasions; the first scan at 20 (range 17-22) weeks and second scan at 30 (range 27-34) weeks gestation. Two experienced ultrasonographers using a Philips IU22, Philips HDI-5000 or a Philips HDI-300 ultrasound machine undertook measurements. Weight and crown-heel length (CHL) were measured at birth (1 to 7 days of age). CHL were measured to the nearest 1mm using a length board (Ellard instrumentation Ltd.,Seattle, WA). Birth weight was measured in regular calibrated scales. Two investigators measured parental and offspring anthropometries. Standing height was measured using a Holtain stadiometer fixed on the wall, to the nearest 0,1cm. Weight was measured to the nearest 0.1 kg by an electronic scale with parents wearing light clothing without shoes.

All variable were checked for normality. Royston models were fitted to foetal and infant growth measurements to create z-scores for size measurements during growth (14). Linear regression analyses were used to explore the relationships between parental sizes, antenatal and postnatal size of the offspring. Multivariable models included maternal parity, height, and weight, paternal height and weight. Maternal smoking and intake of alcohol were considered, but did not influence on the results. The SAS software version 9.1 (SAS Institute, Inc. NC, USA) was used for data analyses, and p-values < 0.05 were considered as significant.

Results

Characteristics of the participants are shown in Table 1. The mean (standard deviation (SD)) maternal height and weight were 164.3 cm (SD = 6.7) and 76.9 kg (SD = 15.5), while the paternal height and weight were 177.7 cm (SD = 7.2) and 86.9 kg (SD = 14.1). At 20 weeks gestation, the foetal FL was 31.6 mm (SD = 2.5), while at 30 weeks gestation FL was 57.9 mm (SD = 3.4). The birth length was 51.0 mm (SD = 2.1) and birth weight 3.53 kg (SD = 0.45).

In 400 foetuses at 20 weeks gestation, each SD rise in maternal weight (of 15.5 cm) was associated with 0.14 SD (0.35 mm) longer FL adjusted for maternal height, paternal height and weight ($p = 0.03$) (Table 2, Figure 1). At 30 weeks gestation, each SD rise in maternal weight was associated with 0.22 SD (0.75 mm) longer FL, adjusted for same covariates ($p < 0.001$). The foetal FL did not differ significantly between female and male foetuses ($p = 0.92$ at 20 weeks, $p = 0.08$ at 30 weeks gestation).

Birth weight and birth length differed between girls and boys ($p = 0.03$ for birth weight, $p < 0.001$ for birth length). In girls, birth weight was associated with maternal height, maternal weight and paternal height in univariate analyses (Table 2). However, in multivariable models, only maternal height persisted significant, and each SD rise in maternal height (of 6.7 cm) was associated with 0.22 SD (99 gram) higher birth weight adjusted for other parental proportion ($p < 0.01$). In girls, birth length was associated with maternal height and paternal height in univariate analyses. While in multivariable models, only paternal height persisted significant, and each SD rise in paternal height (of 7.2 cm) was associated with 0.29 SD (6.1 mm) longer birth length ($p < 0.01$, Table 2, Figure 2).

In boys, birth weight was associated with maternal height and maternal weight in univariate analyses (Table 2). However, in multivariable models, only maternal height persisted significant, and each SD rise in maternal height (of 6.7 cm) was associated with 0.32 SD (144 gram) higher birth weight ($p < 0.001$). In boys, birth length was associated with maternal height, maternal weight and paternal height in univariate analyses. In multivariable models, only maternal height persisted significant, and each SD rise in maternal height was associated with 0.30 SD (6.3 mm) longer birth length ($p < 0.01$, Table 2, Figure 2).

Discussion

Maternal proportions determined early foetal growth, with no effect of paternal proportions here. The main finding is that maternal height is the most important contributor to birth weight, in both sexes, independent of maternal weight and paternal size. In sex-stratified analyses, birth length in girls was determined by paternal height, not maternal height. While birth length in boys, was determined by maternal height, not paternal height.

The association between maternal height and birth length in boys can be explained by maternal constraint based on the fact that boys often grow faster and become larger than girls (15). The mother may therefore need to constrict growth more in boys than in girls, for her own survival (15-17). There is some disagreement about the mechanism behind maternal constraint. Possible explanations that have been suggested are i) maternal regulation of foetal nutrition, ii) maternal hormone regulation or iii) it may involve cytoplasmic inheritance? (18). The theory concerning cytoplasmic inheritance suggests that the ovum contain growth-regulating substances that will reflect the size of the mother and determine foetal size at birth (18). Brooks et al studied the role of environment versus genetic factors in the determination of birth weight following ovum donation (6). They used donor eggs and implanted them, after birth they reported that birth weight was significantly correlated with recipient traits and not the donor traits (6). Therefore the cytoplasmic inheritance alone cannot explain maternal constraint in foetal life. If this was the case, the donor traits, not the recipient's traits, should have been reflected in the offspring.

An alternative explanation for maternal constraint involves imprinting of genes and the conflict theory (15). Reik et al. reported from studies on mice that there are several imprinted genes that play an important role in regulation of foetal growth (15). In general, Reik et al described that paternally expressed genes enhances the foetal growth while maternally expressed genes suppress foetal growth (15). This is linked to the insulin and insulin-like growth factor system (IGF), where IGF-2 is expressed by a paternal gene that is enhancing foetal growth while maternally expressed IGF2-receptor, which is a suppressor of foetal growth (18). This give rise to the conflict theory were the mother wants to down-regulate foetal growth to avoid difficulty at parturition and wish to share resources between offspring. The father on the other hand, strives to extract more resources and maximize the offspring growth. Several studies have shown that a large amount of the imprinted genes that influence foetal growth works in such an antagonistic manner (18). Most of this evidence is from studies on mice, but Hall et al. claims there are plenty of evidence for this also in humans (16). They summarize this evidence in the following six points for mammalian genomic imprinting; i) pronuclear transplantation-type experiments in mice, ii) phenotypes of triploids in humans, iii) expression of certain chromosomal disomies in mice and humans, iv) phenotypic expression of chromosomal deficiency in mice and humans, v) expression of transgene genetic material in transgenic mice and vi) expression of specific genes in mice and humans.

One previous study reported that maternal weight had a greater impact than paternal weight, on offspring birth weight (10). While the maternal and paternal weight and height contribute similarly to offspring weight gain after birth. (10). In this current study, the theories of maternal constraint fits with our findings, where maternal traits have the most important effect on birth weight. However, when we studied birth length we were surprised to discover that paternal height predicted birth length in girls, with no independent effect of maternal height. In contrast, maternal height predicted birth length in boys, with no independent effect of paternal height. We do not know what the reasons for these finding could be. We speculate and suggest that boys with their tendency to grow bigger than girls need to be more “constrained” by the mother, and therefore less susceptible to paternal influence. While girls with lower average birth weight and length are less influenced by maternal constraint and therefore more influenced by paternal size. Harvey et al. reported that paternal height were stronger associated with bone mineral density in new-born girls than in boys, and this effect was also independent of maternal influence (20). Romano et al. reported that male mice were more adversely affected than females, after foetal growth restriction by bilateral uterine vessel ligation (21). Their findings suggest a sex-specific programming of outcomes, as deficits were corrected by postnatal nutrition for females born small, but not for males.

Strength of this study is the relative large sample size and that the participants’ proportions are not self-reported, but measured by investigators. However, the study also has limitations. We have not assessed the inter-observer variability between the two ultra-sonographers. The measurements of birth length can sometimes be challenging to do accurately, so there may be some measurement errors. The participants where multicultural, from all countries all over the world, and we have not accounted for ethnicity in the analyses of the data.

Conclusion

Maternal proportions determined early foetal growth while paternal proportions had no effect on early foetal growth. In sex-stratified analyses, birth length in girls was determined by paternal height, not maternal height, while birth length in boys was determined by maternal height, not paternal height. These findings of sex-differences, where maternal height predicts birth length in boys, and paternal height predicts birth length in girls, need to be further explored and confirmed in other studies. Further investigation of prenatal growth and postnatal growth, and how this can be improved may lead to prevention of adult diseases.

Table 1: Maternal, paternal and offspring characteristics.

Mothers (n = 370)	Mean (SD)	Range
Height (cm)	164.3 (6.7)	145.0-188
Weight (kg)	76.9 (15.5)	46-140
Fathers (n = 345)		
Height (cm)	177.7 (7.2)	158.4-198.5
Weight (kg)	86.9 (14.1)	48-131
Offspring		
Foetal age (20 weeks) (n = 400)	19.5	17-22
Femur length (mm) (n = 399)	31.6 (2.5)	23.3-40.8
	30.0	27-34
Foetal age (30 weeks) (n = 356)		
Femur length (mm)	57.9 (3.4)	50.1-68.2
	39.6 (1.2)	37.0-42.2
Newborn (n = 326)		
Birth length (cm)	51.0 (2.1)	45-57.8
Birth weight (kg)	3.53 (0.45)	2.25-4.80

Table 2: Parental predictors of foetal femur length and new born size (z-score).

	All		Girls		Boys	
Femur Length 20 wk (z-score)	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Maternal Height	0.11*	0.05	0.11	-0.00	0.11	0.06
Maternal Weight	0.17***	0.14**	0.21**	0.17	0.21**	0.20*
Paternal Height	0.04	-0.02	0.03	-0.02	0.00	-0.06
Paternal Weight	0.05	0.02	0.10	0.09	0.001	-0.03
Femur Length 30wk (z-score)						
Maternal Height	0.18***	0.08	0.19**	0.09	0.15*	-0.02
Maternal Weight	0.27***	0.22***	0.20**	0.11	0.29***	0.32***
Paternal Height	0.11*	0.05	0.145	0.07	-0.13	0.11
Paternal Weight	0.10	0.01	0.08	0.01	0.08	-0.03
Birthweight (z-score)						
Maternal Height	0.35***	0.29***	0.32***	0.22**	0.39***	0.32***
Maternal Weight	0.30***	0.13*	0.27***	0.13	0.37***	0.17
Paternal Height	0.21***	0.08	0.27***	0.15	0.15	0.05
Paternal Weight	0.09	-0.01	0.11	-0.05	0.09	0.00
Birth Length (z-score)						
Maternal Height	0.27***	0.22***	0.19*	0.07	0.36***	0.30**
Maternal Weight	0.15**	0.02	0.12	0.02	0.22**	0.08
Paternal Height	0.23***	0.18**	0.25**	0.29**	0.22**	0.13
Paternal Weight	0.04	-0.08	-0.02	-0.19	0.14	0.03

*p < 0.05, ** p < 0.01, *** p < 0.001.

The numbers are standardized estimates in multivariable linear regression analyses.

Adjusted models included maternal parity, age, height, weight, paternal height and weight.

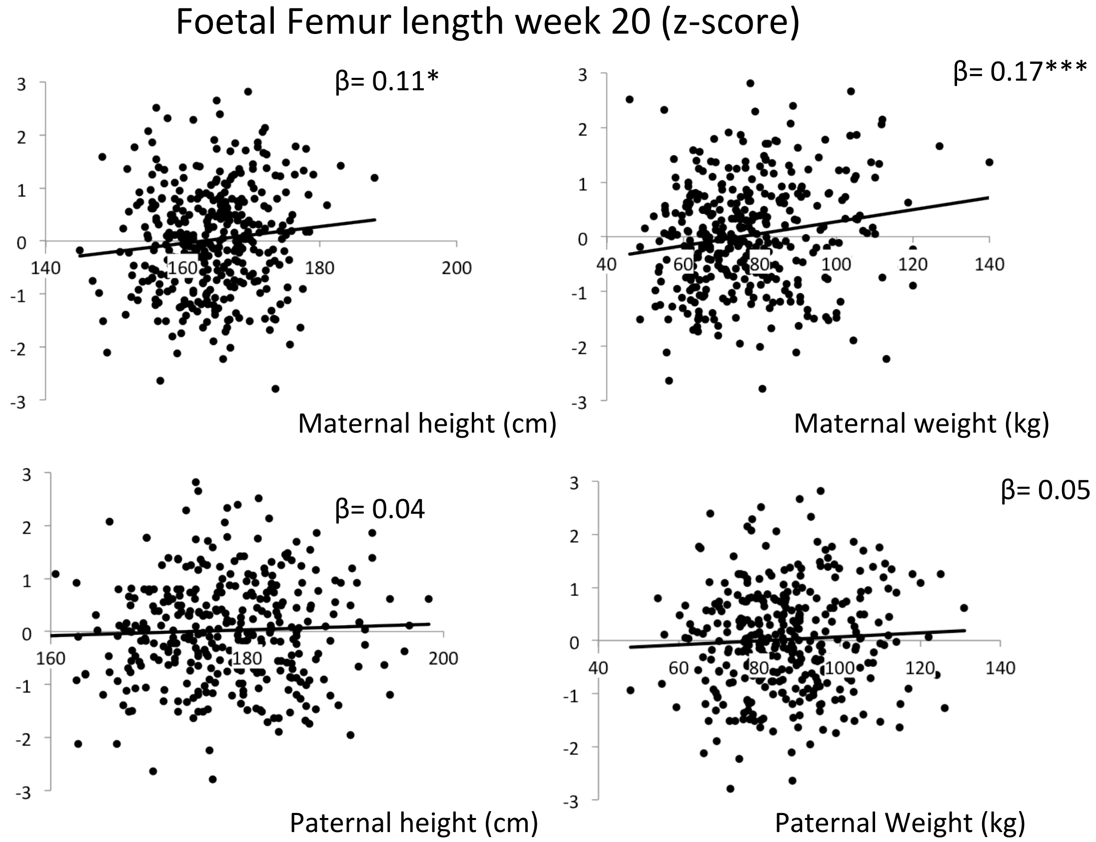

Figure 1.

Foetal femur length at 20 weeks gestation was significantly associated with maternal height and weight, but not by paternal height and weight in univariate analyses.

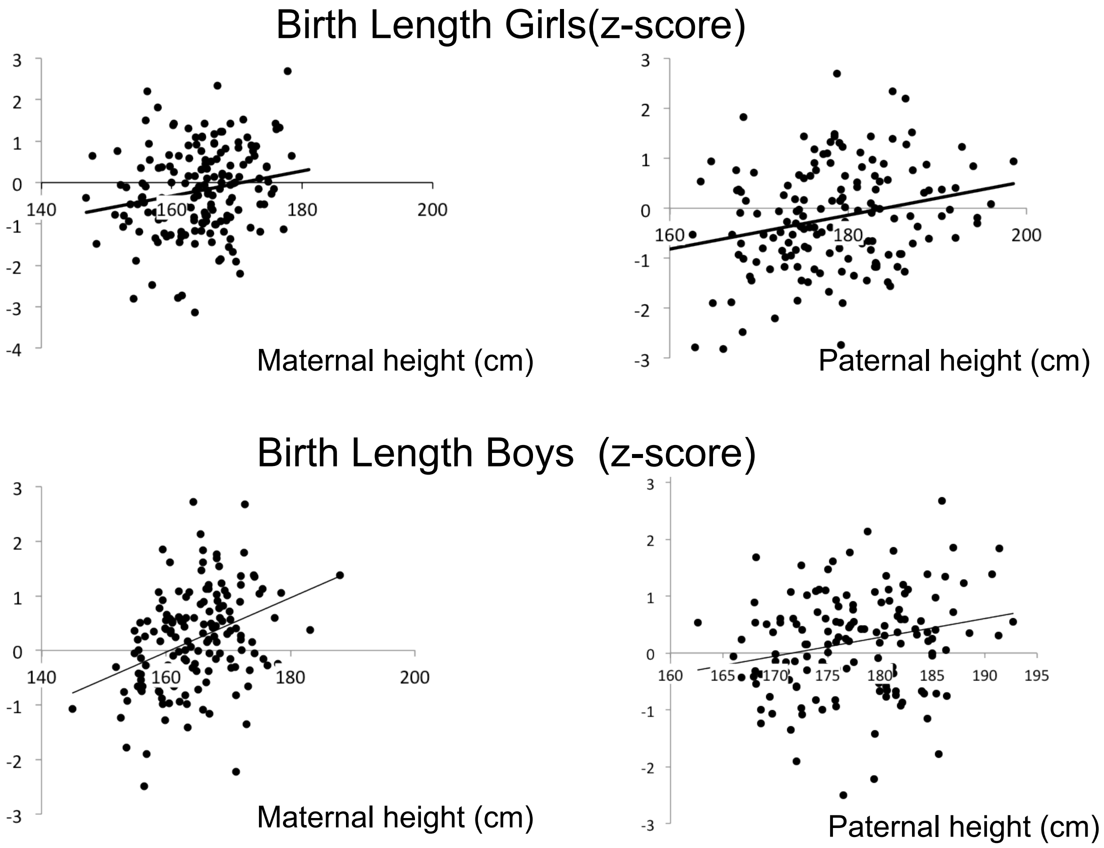

Figure 2.

In girls, birth length was associated with maternal and paternal height in univariate analyses, but only paternal height persisted significant in multivariable models (upper panel). In boys, birth length was associated with maternal and paternal height in univariate analyses, but only maternal height persisted significant in multivariable models (lower panel, see Table 2).

References

1. Barker DJP. The foetal and infant origins of adult disease. BMJ. 1990;301(6761):1111.

2. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Foetal nutrition and cardiovascular disease in adult life. Lancet. 1993;341(8850):938-94.

3. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1): 61-73.

4. Henriksen T, Haugen G, Bollerslev J, Kolset SO, Drevon CA, Iversen PO, and Clausen T. [Foetal nutrition and future health]. Tidsskr.Nor Laegeforen. 2005;125(4),442-444.

5. Brooks AA, Johnson MR et al. Birth weight: nature or nurture? Early Hum Dev 1995;42: 29-35

6. Godfrey K, Walker-Bone K, Robinson S, Taylor P, Shore S, Wheeler T, Cooper C. Neonatal bone mass: influence of parental birth weight, maternal smoking, body composition, and activity during pregnancy. J Bone Miner Res 2001;16:1694-703.

7. Gluckman PD, Hanson MA. Maternal constraint of foetal growth and its consequences. Semin Foetal Neonatal Med 2004;9:419-25.

8. Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. Eur J Endocrinol. 2004;151,Suppl 3:U131-9.

9. Walton A, Hammond J. The maternal effects on growth and conformation in Shire horse-Shetland Pony crosses. Proc R Soc Lond B 1938;135:311-35.

10. Wilcox MA, Newton CS, Johnson IR. Paternal influences on birthweight. Acta Obstet.Gynecol.Scand. 1995;74(1):15-18.

11. Griffiths LJ, Dezateux C, Cole TJ. Differential parental weight and height contributions to offspring birthweight and weight gain in infancy. Int J Epidemiol. 2007;36(1):104-7.

12. Magnus P, Gjessing HK, Skrondal A, Skjaerven R. Paternal contribution to birth weight. J Epidemiol Community Health. 2001;55(12):873-7.

13. Morrison J, Williams GM, Najman JM, Andersen MJ. The influence of paternal height and weight on birth-weight. Aust NZ J Obstet Gynaecol. 1991;31(2):114-116.

14. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound Obstet.Gynecol. 1998;11(1):30-38.

15. Reik W, Walter J, Genomic Imprinting: Parental influence on the genome. Nat Rev Genet. 2001;2(1):21-32.

16. Hall J. G. Genomic imprinting: Review and relevance to human disease. Am J Hum Genet. 1990;46(5):857–873.

17. Moore T, Haig D. Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet. 1991;7(2):45-9.

18. Marshak A. Growth differences in reciprocal hybrids and cytoplasmic influence on growth in mice. 1936;72(3):497–510.

19. Reik W, Davies K, Dean W, Kelsey G, Constância M. Imprinted genes and the coordination of foetal and postnatal growth in mammals. Novartis Found Symp. 2001;237:19-42.

20. Harvey N.C, Javaid M.K, Paternal skeletal size predicts intrauterine bone mineral accrual. J Clin Endocrinol Metab. 2008;93(5):1676-81.

21. Romano T, Wark JD, Owens JA, Wlodek ME. Prenatal growth restriction and postnatal growth restriction followed by accelerated growth independently program reduced bone growth and strength. Bone. 2009;45(1):132-41.