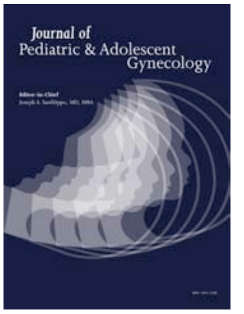
Accepted Manuscript



Hormonal state comparison (progesterone, estradiol and leptin) of body fat and body mass indices in mexican women as a risk factor for physiologic condition neonatal

Magdalena Aguilar, M.Sc Oscar R. Galicia, Ph.D Ulises Aguilera, Ph.D Carlos Varea, Ph.D Cristina Bernis, Ph.D Georgina I. García López, Ph.D

PII: S1083-3188(14)00252-6

DOI: 10.1016/j.jpag.2014.06.007

Reference: PEDADO 1734

To appear in: *Journal of Pediatric and Adolescent Gynecology*

Received Date: 7 November 2013

Revised Date: 30 May 2014

Accepted Date: 30 June 2014

Please cite this article as: Aguilar M, Galicia OR, Aguilera U, Varea C, Bernis C, García López GI, Hormonal state comparison (progesterone, estradiol and leptin) of body fat and body mass indices in mexican women as a risk factor for physiologic condition neonatal, *Journal of Pediatric and Adolescent Gynecology* (2014), doi: 10.1016/j.jpag.2014.06.007.

HORMONAL STATE COMPARISON (PROGESTERONE, ESTRADIOL AND LEPTIN) OF BODY FAT AND BODY MASS INDICES IN MEXICAN WOMEN AS A RISK FACTOR FOR PHYSIOLOGIC CONDITION NEONATAL.

Magdalena Aguilar M.Sc.[1], Oscar R Galicia Ph.D[2], Ulises Aguilera Ph.D [3], Carlos Varea Ph.D [4], Cristina Bernis Ph.D.[5], Georgina I García López Ph.D.[6]

1 Campus Atlacomulco, Autonomous University of the State of Mexico (UAEM).

2 Psychology Department, Iberoamerican University in Mexico City. E-mail:

3 Laboratory of Animal Behavior, Faculty of Sciences, Autonomous University of the State of Mexico.

4 Physical Anthropology Department, Faculty of Sciences, Autonomous University of Madrid (Spain).

5 Physical Anthropology Department, Faculty of Sciences, Autonomous University of Madrid (Spain).

6 Full-time lecturer. Campus Atlacomulco, Autonomous University of the State of Mexico.

Conflict of interest

On behalf of all of the authors, and with their full consent, I warrant that the authors have no conflicts of interest to disclose

Correspondence autor: Magdalena Aguilar Moreno Address. Instituto Literario #100 Colony Centro. Zip Code 50000. Toluca México. E-mail: biomadeleine@gmail.com. Telephone number (+52)17223584218. or (+52)7221995991.

ABSTRACT

Study Objective: Describe the impact of teen pregnancy on later ovarian activity and metabolic hormones considering the concentration of current levels of ovarian steroids and leptin in a sample of Mexican females.

Design: Cross-sectional study in the maternity of the General Hospital of Atlacomulco and campus of the Autonomous University of the State of Mexico (UAEM).

Participants: 71women between the ages of 18 and 24, and 160 neonates seen between March 2010 and June 2012.

Main Outcome Measure(s): The measurements obtained included anthropometric body composition (bioelectrical impedance), serum hormone quantification of ovarian steroids and leptin (immunoassays), and the apgar scores, height and weight in neonates. Statistical analysis included Anova, Student, Pearson and Chi square for $p < 0.05$.

Results: Adolescent mothers showed significantly lower concentrations of estradiol ($p = 0.001$) and progesterone ($p = 0.001$). However, higher levels of leptin in adolescent mothers were not statistically different compared with older mothers ($p = 0.84$). Also, leptin was correlated with all measures of adiposity. The mean birth weights ($p = 0.001$) and Apgar scores ($p = 0.001$) were lower in neonates of adolescent mothers than in neonates of adult mothers. There was no association between maternal age with the anthropometric variables studied.

Conclusions: Early reproduction represents a metabolic stress condition that modifies the long term ovarian activity and metabolic hormones, and impacts the morbi-mortality of the mother and offspring in a later vital life cycle stage.

Key Words: Leptin, adolescent pregnancy; metabolic stress, neonate

INTRODUCTION

Gestation is possibly the most important factor to define reproductive success in human females, and is one of the most decisive for natural selection. It represents the life stage with the highest energy and nutrient demand[1-2]. The energetic situation of women before pregnancy dictates the actual energy requirements necessary to meet the demands of gestation and lactation physiology (i.e., fetal growth, maintenance and growth of maternal tissues, accumulation of adipose tissue, milk synthesis, and maintenance metabolism of mammary glands)[3]. However, being young (≤ 19) during the first reproductive cycle (defined as pregnancy and lactation) adds additional costs associated with poor pregnancy, particularly those occurring two years after menarche. Authors have exhibited that young women, particularly adolescent girls, show strong links between maternal and fetal competition towards growth and development[4-5].

In relation to other hominids, human puberty is a long and particularly sensitive stage of the life cycle in which two physiologically important tasks must be completed: growth and maturation of adult reproductive characteristics. During this stage, pregnancy could lead to a compromising metabolic situation, since scarce resources will be required simultaneously. This dilemma forces the body to make a change in energy allocation towards reproductive effort[6].

Adolescent pregnancy is considered a health problem due to the increased incidence of maternal conditions, perinatal and the neonate when compared with adult mothers, such as anemia, hypertensive status and gestational diabetes, mellitus, eclampsia, a higher number of abortions, cesarean birth and prolonged labor, fetal growth restriction (FGR), low birth weight (LBW), low Apgar scores, undernourishment, prematurity, and perinatal death.[7,8]

Leptin is found between hormones that have a major role in reproductive health. It is a hormone mainly secreted, but not exclusively, by adipose tissue and in women with normal weight it is essentially related with gluteofemoral fat.[9] Evidence supports the complex interrelationship between energy metabolism and female fertility because it exerts its actions essentially at four levels. The first is the central effect on the hypothalamus with a gonadotropin releasing hormone (GnRH) and the hypophysis, or the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).The second level is the peripheral effects in the ovary, endometrium and reproductive tract. The third level is the direct effects on the development of the oocyte and the embryo and the fourth level is the effects during pregnancy to regulate oscillations of levels LH and estradiol preparing the body for the metabolic demands of pregnancy.[10, 11] In turn, the circulating leptin levels in vivo are modulated by a series of factors such as insulin and its more potent regulator, and its main secretagogue, nutrients availability, and triglycerides. Also, the glucocorticoids—especially cortisol, androgens (testosterone) and growth hormone[9,12]—are jointly involved in glucose homeostasis, adipose tissue homeostasis, bone metabolism, food intake,[13] in regulating of the immune system[14] and in the growth hormone/insulin-like growth factor axis (GH / IGF-1).[15] They also have a direct role in steroidogenesis through the metabolic actions of insulin and IGF-I in the human cells of granulosa and theca. These cells contribute to the increase in lipid oxidation which favors during adolescence and under the influence of increasing levels of estradiol, fatty acid storage in the gluteofemoral omega-3 type, which is critical in the brain development[9,16]. This suggests that the scarcity of these fatty acids, and not of the adolescence status per se, may be associated with some cognitive deterioration in the progeny. It is imperative to consider that early motherhood is a physiologic event that also increases the demand of nutrients during adolescence, and that nutritional requirements seem to depend less on chronological age and more on whether growth continues or has ceased.[19]

The superposition of a pregnancy during this vital stage, in which adolescents have higher energy and nutritional requirements, leads to a situation where the needs of both the mother and the fetus cannot be adequately and simultaneously satisfied. Therefore, there is a higher risk that the pregnant adolescent and her fetus will compete for available nutrients. This competition leads to metabolic stress for both the mother and her progeny due to a deficit in the energetic intake or energetic reserves.[20] Epidemiological studies have established a relationship between reduced growth in early life (e.g., pregnancy, lactation, infancy and early childhood) with multiple endocrine dysfunctions in adulthood mainly related to glucose tolerance, insulin resistance[21, 22], hypertension and vascular damage, resistance to growth hormones, and others associated with the metabolic syndrome.[23, 24] "The programming of fetal life" hypothesis is commonly used to explain the development of these alterations in the long-term. This hypothesis proposes that intra-uterine undernourishment triggers endocrine adaptations during critical or sensitive periods of the development, and causes permanent changes in morphology, physiology and metabolism. Also, this could become harmful during periods of abundant nutrition, which is called "developmental plasticity as cause of adult disease".[25]

Therefore our prediction is that the adolescent mothers have a conflict in energetic allocation, and that having not reached its full development of body condition will result in lower fatty deposits (long chain polyunsaturated) in breast and gluteofemoral fat which can impact hormonal status, weight and neonatal physiologic condition. In the present study we quantified hormonal status (progesterone, estradiol and leptin), nutritional status (i.e., weight, body mass and percentage fat mass) of women (adolescents and adult) and the physiologic condition of neonates (i.e., birth weight, birth length and Apgar scores at one and five minutes).

MATERIAL AND METHODS

Seventy-one females (aged 18–24 years) living in Atlacomulco in the State of Mexico were enrolled in this study between 2010 and 2011. Most of the participants were students at the Atlacomulco campus of the Autonomus University of the State of Mexico or employees (general and administrative assistants) at the general hospital in the same geographic region. The women participating in the study signed a consent form after they were informed of the objectives, benefits, and requirements of the research. The study protocol was approved by the ethics committee of the Municipal Bicentenario Hospital following the ethical principles for medical research in humans.

The female participants were divided into four groups based on their chronological age and their age at the time of their first full-term birth: (A) 24 nulligravid adolescents (ages 18–19); (B) 23 nulligravid young adults (ages 20–24); (C) 12 with adolescent primiparity (ages 20–24 but with a full-term pregnancy before age 18); and (D) 12 with young adult primiparity (ages 20–24 with a full-term pregnancy at age 18 or older). The selection criteria for the participants were as follows: regular menstrual cycles with an average duration of 28 ± 7 days; absence of any gynecological, endocrine, or chronic-degenerative condition (*e.g.*, diabetes, hypo/hyperthyroidism); more than six months since the last pregnancy or lactation; no use of steroid-based contraceptives; clinically healthy with a normal weight for their height; and acceptable nutritional status based on their body mass index. The classifications proposed by the World Health Organization (WHO) and the Mexican Official Standard NOM-174-SSA1-1998 were used as a reference. As proposed by the United Nations Development Program in Mexico, to minimize bias, all selected participants were residents of the mixed municipality (rural, urban, and semi-urban) of Atlacomulco in the State of Mexico. The participants were medium-marginalized as graded by the National Population Commission[26] and were from the low–middle socioeconomic stratum according to the Mexican

National Institute of Statistics, Geography, and Informatics and the National Survey of Income and Expenditure of Households [27]. As a population, they were very representative of a large portion of Mexican society. The women included in the study did not belong to any local ethnic group, had an average educational level of 10.5 years, and an average monthly income of two minimum salaries, which is set to the equivalent of US$4.80 per day by the National Commission of Minimum Salaries in Mexico

Anthropometric variables

An anthropometric evaluation was performed according to criteria established by the (WHO)[28] for their weight and the percentage of body fat registered with a low-intensity impedance meter (500 µA, 1 mA; accuracy 0.1%); height, obtained with a portable stadiometer (accuracy 1.0 mm); and body mass index (BMI), calculated by dividing weight (kg) by height^2 (m), which is considered an indicator of the balance in bodily functions. The waist/hip ratio (WHR) is another useful anthropometric measurement utilized specifically to describe the accumulated fat in the hips. This ratio relates the circumference of the waist at the last floating rib to the maximum hip circumference at the level of the gluteus. The circumferences were obtained using a 1-m long × 0.5-cm wide flexible measuring tape with an accuracy of 1 mm.

Hormone analysis

The quantitative measurements of ovarian function included the average estradiol and progesterone serum levels as determined by immunoassays throughout an entire menstrual cycle. Every other morning 3 mL of blood was collected by peripheral venipuncture and placed in tubes without coagulant. After natural coagulation, the samples were centrifuged, and the serum was collected. Several methods are used to infer the ovulation period, but for operational reasons before the statistical analysis, ovulation was assumed when follicular progesterone levels at least two standard deviations above the average. The cycles were aligned to day 0 based on the mid-point in the cycle when the plasma estradiol levels reached a minimum. This coincides with the beginning of a raise in the luteal progesterone level, which provides a reasonable estimate of the first day of ovulation. Seven quantitative indices of the estradiol, progesterone and leptin serum levels were calculated for each menstrual cycle: average estradiol, average follicular estradiol, average ovulatory estradiol, average luteal estradiol, average progesterone (ng/mL) during the last 14 days of the menstrual cycle follicular leptin (ng/mL -14 to -1 days) and luteal leptin (ng/mL +1 to +14 days). The hormone levels were determined by enzyme immunoassays using a commercial kit by Diagnostic Systems Laboratories, Inc. (Webster, Texas, USA). These levels were measured by an enzyme immunoassay (EIA) using a commercial kit by DSL (Diagnostic Systems Laboratories, Inc. Texas), determined by the automated analyzer IMMULITE 2000 (Diagnostics Product Corporation (DPC), Los Angeles, CA, USA).Comparisons were restricted to the samples with ovulatory cycles, because the inclusion of anovulatory cycles would lower the mean hormone levels estimates [29] .

Variables of the newborn

For the analysis we only considered 103 neonates whose births occurred in the maternity of the public General Hospital of Atlacomulco. Newborns whose mother presented potentially influential complications during pregnancy—such as hypertension, under-nutrition, smoking, insulin-dependent diabetes, or multiple gestation—or newborns with congenital anomaly were excluded. Measurement of the newborn was taken within 12 hours of delivery by a pediatric nurse using standard techniques.

Birth weight for neonatal weight categorization we considered the classification proposed by the WHO.

Apgar scores that vary between 1 and 10 were calculated at one and five minutes to evaluate the tolerance level of the birth process, adaptability to the environment and the resilience of the newborn. A score of 7 – 10 is considered normal, 4 – 7 intermediate, and 0 – 3 poor where the infant requires immediate resuscitation.

Birth length (cm) was measured from the crown of the head to the heel.

Gestational age was based on the mother´s obstetric history and was defined as the number of completed weeks from the first day of the last menstrual period to the date of birth. The newborns were classified according to their gestational age.

Premature infants are defined as those born before 37 weeks.

Mature infants are defined as born within thea normal pregnancy can range from 38 to 42 weeks.

Postmature infants are defined as those born after 43 weeks.

Ethical considerations

The women participating in the study signed a consent form after they were informed of the objectives, benefits and requirements of the research. The study protocol was approved by the ethics committee of the Municipal Bicentenario Hospital, following the ethical principles for medical research in humans.

Statistical analysis

Statistical analyses were performed with SPSS for Windows. Kolmogorov-Smirnov tests were used to verify the normality of variables. The comparisons of the basic characteristics (age at menarche, weight, height, BMI, and WHR) were made by performing an unpaired t test. Differences in hormone concentrations, anthropometric characteristic between groups were compared through an analysis of variance (ANOVA) test followed by a post-hoc Tukey test . Chi-squared (χ^2) tests were performed on the categorical data regarding the use of tobacco and alcohol. The effects of anthropometric variables were tested by a simple linear regression model. A *P*-level <0.05 was considered statistically significant.

RESULTS

General characteristics and body composition

There were no statistically significant differences between the four groups in the factors that could potentially influence the hormone levels during the menstrual cycle such as age at menarche, menstrual cycle length, and frequency in the use of tobacco and alcohol. It should be noted that among the three groups excluding the nulligravid adolescents, there were no significant differences in the age groups. The time since the last pregnancy and the age at first pregnancy and birth were the two factors that showed statistically significant variation. Table 1 shows the general characteristics of the women classified according to their reproductive status.

Hormone analysis

Analysis of the ovulatory cycle revealed differences in serum levels of estradiol (F= 6.68, P=0.001) and progesterone (F= 6.66, P= 0.001) between groups. Values were significant in nulligravid adults, primiparous young adults and nulligravid adolescents (65%, 53% and 16%, respectively) compared with adolescent primiparity (young adults who conceived as adolescents) throughout the menstrual cycle. However, they did not differ in any of the parameters including anthropometric, age or lifestyle. Contrast analyses showed that the differences in average estradiol levels were statistically significant between the nulligravid young adults and nulligravid adolescents (*P* = 0.006); the nulligravid young adults and adolescent primiparity (*P* = 0.001); and the teenage mothers and young adults mothers (*P* = 0.045). In contrast, there were no significant differences for any of the indices between the young adults with adolescent primiparity and nulligravid adolescents; the nulliparous young adults and primiparous young adults; or the primiparous young adults and nulligravid adolescents (*P* = 0.757, *P* = 0.914, and *P* = 0.200, respectively). The values were significantly higher in the nulligravid young adults and primiparous young adults (39% and 35%, respectively) than in the young adults with adolescent primiparity, although they did not significantly differ in any other parameters, such as the anthropometric variables, chronological age, and lifestyle. The same trend was seen for the progesterone levels, which were significantly lower in the teenage mothers in comparison to the primiparous young adults who conceived as adults, nulligravid young adults, and nulligravid adolescents (*P* = 0.001).

Leptin concentrations increased from the early follicular phase and decreased in the days surrounding the peri-ovulatory phase. We found this profile for both adolescents and adult mothers, with a higher concentration in adolescent primiparity to contrast it with the group of primiparous young adults (Figure 1) and found no differences between both groups in serum levels of leptin follicular (t = 2.75 P = 0.84) and luteal leptin (t = 1.03 P = 0.38).

Relationships between anthropometric variables and hormonal levels

Simple linear regression models were used to test the effects of the anthropometric variables on the estradiol progesterone and leptin levels as dependent variables or independent predictors; none of the analyzed variables had a significant effect on either ovarian function level (progesterone, estradiol) Table 3. The main predictors of leptin are body weight, body fat percentage, BMI, hip circumference, waist circumference and WHR Table 4.

Neonatal variables

The mean birth weight was 2524.22 ± 908.6 grams. A total of 16.0% of patients were adolescent, 41% young mothers and 43% adult mothers. Mean gestational ages was 37.8 ±5.9 weeks and included 45.5% preterm, 49.1 % term, 85.3% , and only 5.5 % post-term infants. Among the newborns, 42.1% were characterized as low weight, 56.8% were normal weight and 1.1% suffered macrosomia. In the overall group of neonates, there were no significant differences by sex between the different anthropometric variables. Summary measures of weight and anthropometric variable are presented in Table 1. At gestational ages of 37 to 41 completed weeks, newborns of primiparous adolescents had significantly lower mean birth weights than newborns of primiparous adults (*P*=0.049). The mean difference in birth length in full term neonates was not statistically significant (*P*= 0.649). Mean Apgar scores at 1 min were lower in newborns of primiparous adolescents than their counterparts (*P*= 0-001)., but there were no statistically significant differences in Apgar scores at 5 min (*P*=0.72) (Figure 2). Mean gestational age did not differ significantly between the two groups and no differences were found in terms of prematurity. No significant association was found between maternal age and weight, height or Apgar scores at minute 5 of the neonate (*P*=0.173; *P*=0.325; *P*=0.787. respectively). However if it is related to the gestational age, Apgar scores at 1 minute (*P*=0.047) are statistically significant. Until today, it is controversial whether teenage pregnancy is a risk factor; however, various researchers show that the process can be done with results similar to that of adult women, especially if the teenagers are older than 15 years of age.

DISCUSSION

From our results it is clear that early motherhood represents a physiologic model of energy deficiency. Nutritional alterations due to chronic excessive energy expenditure where respond and adapt to the stress factors involve important costs. As metabolic energy is limited, the body must allocate energy resources away from other metabolic tasks that can be postponed to solve the current challenges. The reallocation of energy necessary to respond to these challenges is mediated in part by increased circulating levels of insulin and cortisol. These increased levels are associated with conditions of scarcity or high energetic demand and can provoke to a certain degree an ovarian suppression.[30, 31] There is evidence that the low levels of ovarian function in adolescent primiparity (young adults who conceived as adolescent) regarding the six indices in estradiol and in the luteal progesterone. Ellison[6] have proposed that sensitivity of ovarian function is linked to a comprehensive program of energy allocation that is moderated by assessing environmental impacts such as nutrition, energy expenditure, immune stressors and possibly regulated by metabolic hormones such as insulin, leptin or growth factors that operate directly on the ovarian through the hypothalamus.

Adolescent pregnancy is certainly a situation where they can find feasibly higher cortisol levels can increase the expression of the leptin gene and cause a status of hyperinsulinemia,[12] which can act to stimulate the production of leptin, regardless of changes in the tissue adipose.[9,32] Leptin in turn exerts a predominant role at the level of other neuroendocrine axes as growth hormone endocrine axis (HC/IGF-1) [14], which regulates cell growth in response to energy and nutrients. It also shows the sensitivity to the restrictions in the energetic availability, in collaboration with insulin, which in turn promotes the synthesis and biologic activity of IGF-1 and growth hormone;[7,12] however, in energetic stress conditions there exists a paradox and the insulin exerts opposite effects over the plasmatic levels of the growth hormone which results in a physiologic decrease of the hormonal axis. But in an obesity condition characterized by a positive energy balance, the growth hormone is blocked since there exists high levels of leptin.[33]

Previous human ovarian cell studies have found high concentrations of leptin in adolescent mothers.[35] This effect can result in an insufficient stimulus to reach the (LH) peak that leads to an immature preovulatory follicle and in turn a luteum corpus that is unable to maintain a steady production of progesterone required to keep the fertilized egg in the early stages of implantation or, in an extreme case, the absence of preovulatory follicle.[36] It is even reported that women with polycystic ovary syndrome (PCOS) can produce less potent forms of leptin or have a decrease in the response at the level of the target tissue. So the hyperleptinemia specifically in adolescent mothers may contribute to desensitization of the axis GH / IGF -1, and of the ovarian steroidogenesis. It may also explain the unchanged levels of leptin which also are increased in cases of choriocarcinoma, preeclampsia, type 1 diabetes, mellitus evidence, endometrial and breast cancer, molar pregnancy, and anorexia as similar to patients with fertility disorders, anovulation and endometriosis.[37, 38]

The results of this research as well as previous studies confirm the fluctuation in leptin levels in women with normal weight. In our study, in both adolescent mothers and juveniles there is a match in the pattern of insulin resistance during the menstrual cycle. Schenieder et al [10] reported that there are small but significant variations in insulin levels during the menstrual cycle where concentrations begin to rise before ovulation, with the maximum level occurring during the early luteal phase and gradually decreasing in the late follicular phase. This is positively associated with the variability in the levels of estradiol and progesterone. Even recently it has been suggested that progesterone may induce insulin resistance through the inhibition of insulin signaling in the adipocytes. Although the period of more insulin resistance in the menstrual cycle does not coincide exactly with the maximum levels of estradiol and progesterone during the late luteal phase, it may reveal that both ovarian steroids do not have a joint effect.[39] Our results suggest that pregnancy to term changes the systemic environment, and alters endocrine hormones such as estradiol and progesterone that in turn regulate the signaling of mammary glands , thus reducing the susceptibility of breast tumours.

It is evident that the energetic optimization by the imposition of costs represented by the prolonged investment of gestation and lactation induces adjustments that are energetically costly and difficult to take in adolescent mothers. It has been demonstrated that in the stages of the life cycle, such as puberty and pregnancy in early phases are the status of efficient storage of adipose deposits gluteofemoral and mammary propitious to face situations of gestation and lactation even in periods of caloric restriction and of fatty acids of long chain polyunsaturated (DHA),which are critical for the fetal and infant neurological development.[16-18] Recent studies have even shown that women with acceptable nutrition demonstrate a relative loss of fat gluteus. This is also shown in many undernourished populations. This fat is not replaced and women become progressively thinner in each parity which is called "maternal depletion".[41] However adolescent mothers in our study even under a state of excessive energy expenditure and nutritional disorders do not show a depletion of fat mass with respect to juveniles. This confirms the research by Scholl et al. where adolescents who experience an increase in size during pregnancy had higher concentrations of leptin during pregnancy.[11,42] There is a gradual increase toward the second trimester that relates with a state of reduced sensitivity to the insulin and with the peak of maternal fat accumulation[43, 44], which contributes to the successful development of the fetus. Besides, these increases in leptin show that a positive relation with cortisol and a negative relation with human chorionic gonadotropin (HCG) were maintained and were even overcome in postpartum in comparison with pregnant teens with no growth and in the adult pregnant women.[11,42] Nevertheless paradoxically the peak concentration of leptin in gestation at 28 weeks seems to mark the increase in fat reserves and even until the end of pregnancy is associated with maternal growth, a higher weight gain, and higher retention of postpartum weight with no apparent effect of breastfeed on body composition.[45] So despite the anthropometric changes typically associated with the increase of fetal size, pregnant women seem to not mobilize fat reserves at the end of the pregnancy destined to improve the fetal growth. They instead apparently guard it to cover their own metabolic requirements of growth and development, which results in (LBW) ($\leq$ 2500 g) [46] consistent with the observations of preterm birth, intrauterine growth retardation, lower Apgar scores at least in the 1 (min) and (LBW) in the neonate of the adolescent mothers. This situation is considered as a worldwide priority that impacts all of neonatal and infant mortality.

According to the above, our data allow us to reaffirm the proposed hypothesis of the competition between the metabolic demands of a growing adolescent mother and the nutritional and energetic needs of her fetus in development.[47] It is clear that there is a intraindividual conflict over the energetic physiologic assignation and that the mother in her marginal conditions conserve her own reserves of nutrients in the form of tissue at the expense of fetal growth. This can lead to certain trajectories of development that compromise the health of the mother and her child in later-stages of the vital cycle. Also, this situation may impact adolescents from developing countries more, including Mexico, due to the relative deficit in the preconception nutritional status. This indicates that adolescence is an important event in the reproductive career of women and is linked to acquisition of resources towards a higher reproductive success in the future, where the full maturation is not limited to its ability to menstruate

ACKNOWLEDGEMENTS

We want to express our sincere thanks to all the women who participated in this research, to Dr. Veronica Diaz Perez for her help through it all the study, as well to the Nurse Catherine Atilano for her valuable medical assistance. This study was funded by PROMEP FE26/2009 (103.5/09/4195) and CONACYT.

REFERENCES

1. Stearns SC: The Evolution of Life Histories, Oxford University Press, 1992, pp 249.

2. King JC, Butte NF, Bronstein MN, et al: Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr. 1994; 59(2):4395-4455.

3. Goldman N, Westhoff CF, Paul LE: Variations in natural fertility the effect of lactation and other determinants. Popul Stud. 1987; 41:127-146.

4. King JC, Butte NF, Bronstein MN, et al: Energy metabolism during pregnancy: influence of maternal energy status. Am J Clin Nutr. 1994; 59(2):4395-4455.

5 Scholl TO, Hediger ML, Schall JI, et al: Maternal growth during pregnancy and the competition for nutrients. Am J Clin Nutr. 1994; 60(2):183-188.

6. Ellison PT: Energetics and reproductive effort. Am J Hum Biol. (2003); 15:342-351-

7. Kline J, Stein Z, Susser M. Conception to birth: epidemiology of prenatal development. Oxford University Press, New York.   3. Scholl TO, Hediger ML, Schall JI, et al: Maternal growth during pregnancy and the competition for nutrients. Am J Clin Nutr. 1994; 60(2):183-188.

8. Shapiro C, Sutija VG, Bush J, et al: Effect of maternal weight gain on infant birth weight. J Perinat Med. 2000; 28(6):428–431.

9. Moschos S, Chan JL, Mantzoros CS. Leptin and reproduction: a review. Fertil Steril. 2002; 77(3):433:444.

10. Schneider JE, Zhou D, Blum RM. Leptin and metabolic control of reproduction. Horm Behav. 2000; 37(4): 306-326.

11. Scholl TO, Stein TP, Woollcott KS. Leptin and maternal growth during adolescent pregnancy. Am J Clin Nutr. 2000; 72:1542-1547.

12. Wabitsch M, Jensen PB, Blum WF, et al: Insulin and cortisol promote leptin production in human fat cells. Diabetes. 1996; 45:1435-1438.

13. Wlodarski K, Wlodarski P. Leptin as a modulator of osteogenesis. Ortop Traumatol Rehabil. 2009; 11(1):1-6.

14. Matarese G. Leptin and the immune system: how nutritional status influences the immune response. Eur Cytokine Netw. 2000; 11(1)7-14.

15. Tsai EM, Yang CH, Chen SC, et al. Leptin affects pregnancy outcome of in vitro fertilization and steroidogenesis of human granulosa cells. J Assist Reprod Genet. 2002; 19(4):169–176.

16. Innis SM. Polyunsaturated fatty acids in human milk: an essential role in infant development. Adv Exp Med Biol. 2004; 554:27–43.

17. Lassek WD, Gaulin SJC. Waist-hip ratio and cognitive ability: is gluteofemoral fat a privileged store of neurodevelopmental resources?. Evol Hum Behav. 2008; 29(1):26–34.

18. Cohen JT, Bellinger DC, Connor WE, et al: A quantitative analysis of prenatal intake of n−3 polyunsaturated fatty acids and cognitive development. Am J Prev Med. 2005; 29(4):366–374.

19. Scholl TO, Hediger ML. A review of the epidemiology of nutrition and adolescent pregnancy: maternal growth during pregnancy and its effect on the fetus. J Am Coll Nutr. 1993;12(2):101-107.

20. Lassek WD, Gaulin SJC. Brief communication: menarche is related to fat distribution. Am J Phys Anthropol. 2007; 133(4):1147-1151.

21. Merchant K, Martorell R, Haas J. Consequences for maternal nutrition of reproductive stress across consecutive pregnancies. Am J Clin Nutr. 1990; 52(4):616-620.

22. Must A, Jacques PF, Dallal GE, et al: Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med. 1992; 327:1350-1355.

23. Barker DJP, Gluckman PD, Godfrey KM, et al: Fetal nutrition and cardiovascular disease in adult life. Lancet. 1993;341:938–941.

24. Palmo JR, Rosenberg L, Shapiro S. Reproductive factors and risk of myocardial infarction. Am J Epidemiol. 1992;136:408-416.

25. Barker DJP, Clark PM. Fetal undernutrition and disease in later life. Rev Reprod. 1997; 2:105-112.

26. Consejo Nacional de Población (CONAPO). Índice de Marginación por localidad. Web site. http://www.conapo.gob.mx. Update May 7 2012. Accessed May 20 2013.

27. Instituto Nacional de Estadística y Geografía (INEGI). Encuesta Nacional de Ingresos y Gastos de los Hogares (ENIGH). Web site. http://www.inegi.org.mx. Accessed 2013 May 20.

28. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL. Illinois. Human Kinetics Books. 1988.

29. Vitzthum VJ, Spielvogel H, Thornburg J: Interpopulations differences in progesterone levels during conception and implantations in humans. Proc Natl Acad Sci USA. (2004); 101:1443-1448.

30. Kanaley JA, Hartman MD. Cortisol and growth hormone responses to exercise. Endocrinologist. 2002; 12:421-432.

31. Nepomnaschy PA, Welch K, McConnell D, et al: 2004. Stress and female repro-ductive function: a study of daily variations in cortisol, gonadotrophins, and gonadal steroids in a rural Mayan population. Am J Hum Biol. 2004; 16:523–532.

32. Rosenbaum M, Leibel RL. Leptin: a molecule integrating somatic energy store, energy expenditure and fertility. Trends Endocrinol Metab. 1989;9:117-124.

33. Esteghamati A, Khalilzadeh O, Anvari M, et al: Association of serum leptin levels with homeostasis model assessment-estimated insulin resistance and metabolic syndrome: the key role of central obesity. Metab Syndr Relat Disord. 2009; 7:447-452.

34. Spicer LJ, Chamberlain CS, Francisco CC. Ovarian action of leptin: effects on insulin-like growth factor-I-stimulated function of granulosa and thecal cells. Endocrine. 2000; 12:53–59.

35. Kaaks R. Lukanova A. Energy balance and cancer; the role of insulin and insulin-like growth factor-I. Proc Nutr Soc. 2001; 60(1): 91-106.

36. Karlsson C, Lindell K, Svensson E, et al. Expression of functional leptin receptors in the human ovary. J Clin Endocrinol Metab. 1997; 82(12):4144–4148.

37. Kowalska I, Kinalski M, Straczkowski M, et al: Insulin, leptin, IGF-I and insulin-dependent protein concentrations after insulin-sensitizing therapy in obese women with polycystic ovary syndrome. Eur J Endocrinol. 2001; 144(5):509-515.

38. Bandaru P, Shankar A. Association between plasma leptin levels and diabetes mellitus. Metab Syndr Relat Disord. 2011; 9(1):19-23.

39. Livingstone C, Collison M. Sex steroids and insulin resistance. Clin Sci (Lond). 2002; 102(2):151-166.

40. Horlick MB, Rosenbaum M, Nicolson M, et al. Effect of puberty on the relationship between circulating leptin and body composition. J Clin Endocrinol Metab, 2002; 85(7):2509-2518.

41. Jellife, BD, Maddocks I. Ecological malnutrition in the New Guinea highlands. Clin Pediatr (Phila). 1964; 3:432-438.

42. Scholl TO, Hediger ML, Ances IG. Maternal growth during pregnancy and decreased infant birth weight. Am J Clin Nutr. 1990; 51(5):790-793.

43. Mitchell M, Armstrong DT, Robker RL et al: Adipokines:implications for female fertility and obesity. Reproduction. 2005; 130: 583-597.

44. Karamouti M, Kollia P, Kallitsaris A, et al: Modulating effect of leptin on basal and follicle stimulating hormone stimulated steroidogenesis in cultured human lutein granulosa cells. 2009, 32(5):415-419.

45. Frisancho AR, Matos J, Leonard WR, et al: Developmental and nutritional determinants of pregnancy outcome among teenagers. Am J Phys Anthropol. 1985; 66(3):247-261.

46. Winkvist A, Rasmussen KM, Habicht JP. A new definition of maternal depletion syndrome. Am J Public Health. 1992; 82:691-694.

47. Naeye RL. Teenaged and pre-teenaged pregnancies: Consequences of the fetal-maternal competition for nutrients. Pediatrics. 1981; 67:146-150.

Figure legends

Legend Figure1. Representation of serum leptin concentrations and luteal follicular average (ng / ml) in adolescents and primiparous adult women.

Legend Figure 2. (A). Average neonatal weight (B). Average newborn length (C) Apgar scores at 1 and 5 (min) (D) Gestational age in primiparous adolescents and primiparous adult women.

Table1. Descriptive statics of the study populations

Characteristics	**Adolescent primiparity (ages 20.24) (n=12)**	**Young adult primiparity (ages 20.24) (n=12)**	***P* Value**
Maternal	Mean (SE)	Mean (SE)	
Age (years)	20.0 (1.9)	22.5 (1.6)	0.001[a]
Age at first birth (years)*	16.7 (1.2)	20.7 (1.7)	0.001[a]
Menarche age, (years)	11.2 (3.8)	12.0 (.7)	0.43[b]
Weight (kg)	56.0 (9.5)	54.6 (9.6)	0.67[b]
Height (cm)	157.4 (6.2)	154.5 (5.4)	0.56[b]
BMI	23.4 (4.6)	23.2 (4.4)	0.80[b]
WHR	0.73 (0.08)	0.73 (0.08)	0.82[b]
Body fat (%)	27.2 (7.5)	27.4 (8.4)	0.77[b]
Duration of menstrual cycle (days)	29.45 (2.9)	29.90 (2.4)	0.72[b]
Alcohol use (%)	8.3	9.1	0.221
Tobacco use (%)	8.3	9.1	0.757
Newborn			

Characteristics	**Adolescent primiparity (ages 20.24) (n=12)**	**Young adult primiparity (ages 20.24) (n=12)**	***P* Value**
Birth weight (g)	2286. (41.0)	3389.6 (104.0)	0.001[a]
Birth length (cm)	42.1 (2.67)	50.9 (1.18)	0.03[a]
Gestational age (week´s)	33.3 (4.6)	39.5 (4.4)	0.002[a]
Apgar score 1 minute	7.5 (1.2)	8.0 (0)	0.001[a]
Apgar score 5 minutes	8.8 (3.78)	8.89 (3.33)	0.72[a]

.

	Nulligravid Adolescents (ages 18-19) n=24	**Nulligravid Young adults (ages 20-24) n=23**	***PValue***
Age (years)	18.3 (0.1)	21.6 (0.9)	0.001[b]
Menarche age (years)	12.1 (1.1)	12.6 (1.4)	0.368[b]
Weight (kg)	57.4 (8.5)	57.8 (8.1)	0.872[b]
Height (cm)	156.4 (4.7)	155.1 (4.8)	0.849[b]
BMI (kg/m^2)	23.4 (3.2)	24.0 (3.0)	0.888[b]
WHR (waist cm/ hip cm)	0.72 (0.05)	0.74 (0.06)	0.667[b]
Body fat (%)	25.9 (6.3)	28.4 (5.7)	0.690[b]

	Nulligravid Adolescents (ages 18-19) n=24	Nulligravid Young adults (ages 20-24) n=23	*PValue*
Duration of menstrual cycle (days)	29.1 (5.4)	28.5 (2.1)	0.724[b]
Alcohol use (%)	8.0	17.4	0.221[c]
Tobacco use (%)	8.0	13.0	0.757[c]

*Defined as the mother's age in completed years at the time of delivery.

Differences between primiparous young adults and primiparous adolescents who were pregnant as adolescent were analyzed using an unpaired *t*-test. Results are presented as the average values with standard deviations in parentheses. Statistically significant at *P* level < 0.05.

[b] Unpaired *t*-test

[c] One-way analysis of variance

[d] Chi-squared test

Abbreviations: BMI, body mass index; SE, standard error; WHR, waist-hip ratio

Table 2. Average serum levels of estradiol, progesterone and leptin calculated in each menstrual cycle.

	Adolescent primiparity (ages 20-24) n=12	**Nulligravid adolescents (ages 18-19) n=24**	**Young adult primiparity (ages 20.24) n=12**	**Nulligravid youn adults (ages 20-24) n=23**	***P* Value**
Means estradiol	67.5 (15.0)	58.1 (23.5)	95.8 (34.9)	89.0 (23.7)	0.001
Follicular estradiol	54.6 (28.4)	48.7 (31.1)	84.1 (56.05)	82.1 (45.7)	0.001
Ovulatory estradiol	101.6 (23.3)	87.1 (33.6)	145.7 (76.6)	120.0 (46.1)	0.020
Luteal estradiol	62.9 (33.0)	55.9 (33.6)	82.3 (43.0)	76.8 (27.9)	0.001
Luteal progesterone	5.7 (3.5)	2.7 (1.5)	5.9 (4.7)	5.7 (4.1)	0.001
Follicular leptin	11.1 (5.6)	11.2 (7.8)	13.5 (6.8)	9.6 (4.1)	0.84
Luteal leptin	18.1 (10.9)	23.7 (12.5)	24.2 (18.2)	15.8 (9.5)	0.38

Estradiol (pg/mL) (-14 to +14 days), follicular estradiol (pg/mL) (-14 to -1 days), ovulatory estradiol (pg/mL) (-4 to 0 days), luteal estradiol (pg/mL) (+1 to +14 days), luteal progesterone (ng/mL) (+1 to +14 days). Results are presented as the average values with standard deviations in parentheses. Statistically significant at $P < 0.05$.

Table 3. Analysis of covariance

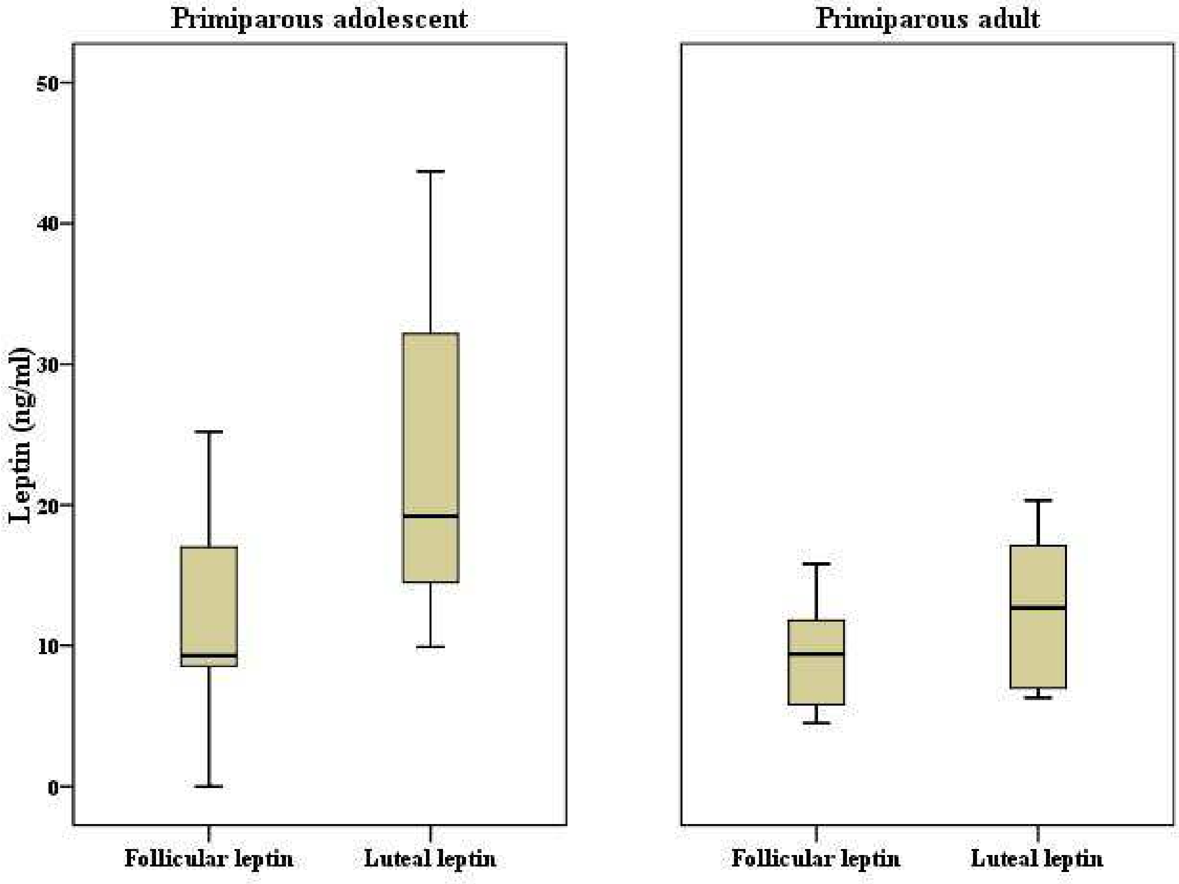
	Average Estradiol		Average Progesterone Luteal	
	R^2	*P*	R^2	*P*
Weight(kg)	0.001	0.911	0.002	0.746
Height (cm)	0.020	0.303	0.015	0.366
BMI (kg/m^2)	0.004	0.641	0.001	0.834
WHR (waist cm/hip cm)	0.018	0.334	0.002	0.725
Body fat (%)	0.009	0.496	0.001	0.945

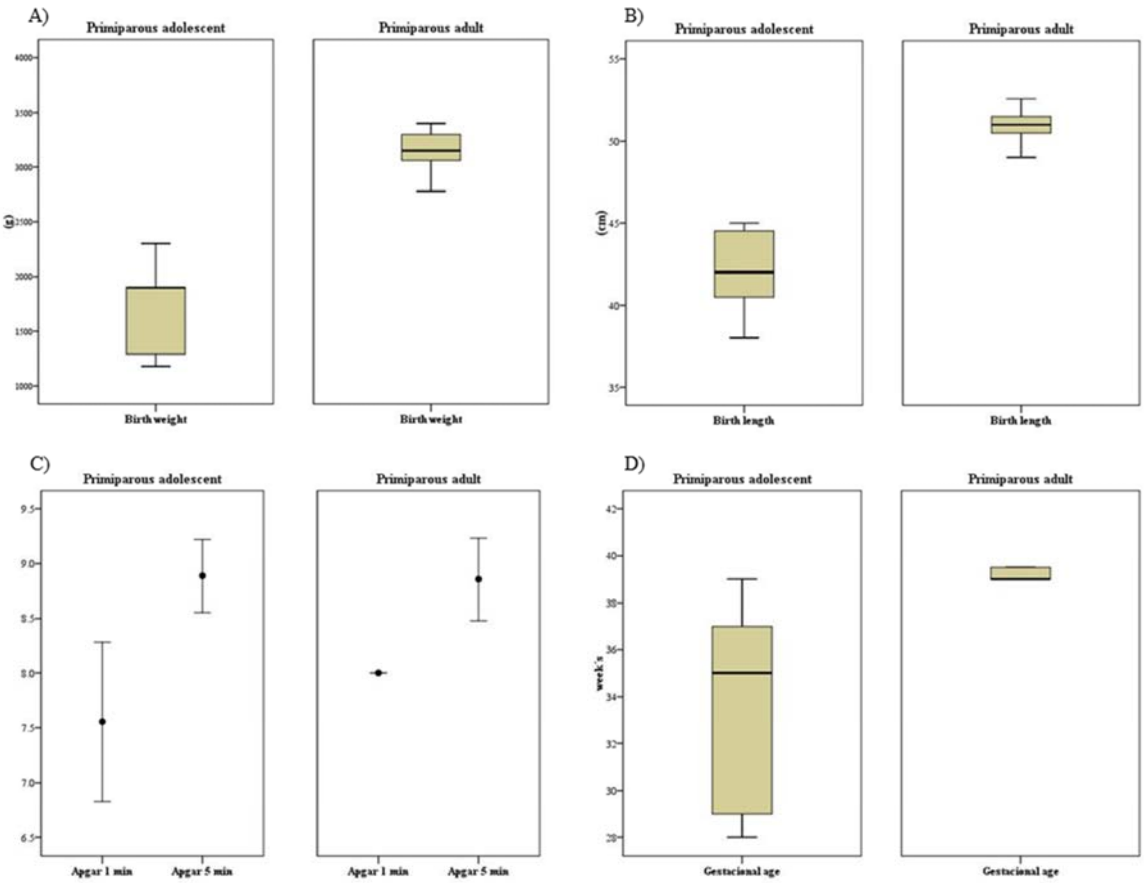
Results of simple regression analysis. Statistically significant at $P< 0.05$.

Table 3. Analysis of covariance.

	Follicular leptin		**Luteal leptin**	
	R	***P***	**R**	***P***
Weight (kg)	0.34	0.007	0.57	0.001
BMI (kg/m^2)	0.37	0.004	0.61	0.001
Waist (cm)	0.35	0.01	0.62	0.001
Hip (cm)	0.30	0.02	0.53	0.001
WHR	0.33	0.03	0.62	0.001
Body fat (%)	0.28	0.03	0.54	0.001

Abbreviations: BMI, body mass index; WHR, waist hip radio. Results of simple regression analysis. *Statistically significant at P< 0.05.


Primiparous adolescent
Primiparous adult
50
40
30
20
10
0
Leptin (ng/ml)
Follicular leptin
Luteal leptin
Follicular leptin
Luteal leptin



A)
Primiparous adolescent
Primiparous adult
(g)
Birth weight
B)
Primiparous adolescent
Primiparous adult
(cm)
Birth length
C)
Primiparous adolescent
Primiparous adult
Apgar 1 min
Apgar 5 min
D)
Primiparous adolescent
Primiparous adult
week's
Gestacional age