

Childhood obesity: Implications In Pubertal Process

ebook.ecog-obesity.eu/chapter-clinics-complications/childhood-obesity-implications-in-pubertal-process



Elpis Vlachopapadopoulou

Pediatric-Endocrinology

Director

Dept. of Endocrinology-Growth and Development

Children's Hospital "P. & A. Kyriakou"

Athens, Greece

elpis.vl@gmail.com

Introduction

Neuroregulation of weight control and pubertal initiation are interrelated. We will examine the factors that regulate appetite and satiety, as well as energy homeostasis and we will elaborate on the influence that these factors exert on the hypothalamo-pituitary-gonadal (HPG) axis system. Leptin plays a key role in this regulation. A minimal amount of body fat is required in order for the pubertal changes to occur and more importantly, a minimal percentage of body fat is a prerequisite for menarche (1,2,3,4). On the other hand, several papers have documented that overweight and obese girls experience menarche at an earlier age as compared to normal weight counterparts. A secular trend towards an earlier age of menarche associated with the improvement of socioeconomic conditions and parallel with the increase of the prevalence of overweight and obesity, has been documented (5,6). The prevalence of premature adrenarche is increasing and is higher among overweight and obese girls than among those with normal weight. A history of premature adrenarche increases the risk of developing polycystic ovary syndrome (PCOS) at a postmenarchal age. Obesity during the transition phase may promote the development of PCOS in adolescence. The prevalence of PCOS is higher among overweight/obese girls than among those with normal Body Mass Index (BMI)(7). PCOS is related to reduced fertility. The use of contraception by obese adolescent girls is of special concern because of an increased risk of adverse events.

Recent articles documented an association between an increased BMI, lower testosterone (T) concentrations and delayed puberty in adolescent boys (8).

Pubertal development

Puberty is the process by which the children develop secondary sexual characteristics and reproductive capacity. The timing and tempo of pubertal development is influenced by many genetic and environmental factors. Nutrition plays a key role as evidenced by the delay of pubertal initiation and primary amenorrhea, as well as pubertal blockade and secondary amenorrhea associated with marked undernutrition. Although the permissive role of adequate nutrition for the activation of the gonadotropin releasing hormone (GnRH) is established, the exact role of overnutrition has not been fully elucidated (9). The initiation of the pubertal process appears to be controlled by the availability of energy, as means to prevent fertility during advert conditions (10). The connecting link between nutrition, adiposity and neurohormonal changes leading to pubertal development is leptin. Leptin, an adipocyte derived hormone, plays a very important role in this process. Leptin levels are very low in states of energy deficit, while they increase in states of energy excess and as body fat mass increases. Leptin is a key metabolic cue that signals energy sufficiency to control adequacy and timing of the reproductive function. In both sexes, leptin levels rise before puberty, followed by a rise of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and subsequently of sex steroids (11,12). The subsequent response of leptin to the sex steroids is sexually dimorphic: while leptin levels increase in response to estrogens, they decrease in response to testosterone (13). Leptin is required but not sufficient for normal sexual maturation as it has become evident from the studies of children with congenital hypoleptinemia in whom the administration of leptin did not trigger puberty (14). GnRH neurons lack leptin receptors and thus leptin itself cannot stimulate GnRH secretion (15). Leptin action is mediated through Kisspeptine secretion, as Kiss1 neurons located in the arcuate nucleus have leptin receptors (10). Besides leptin, neurokinin B, which is co-expressed with Kisspeptine, acts in an autocrine/paracrine action and conveys metabolic information to

Kiss1 neurons thereby contributing to triggering the initiation of puberty (16, 17).

Obesity is characterized by a state of hyperleptinemia secondary to the expansion of the adipocytes together with leptin resistance (18). Hyperleptinemia is associated with hyperinsulinemia, insulin resistance, increased levels of inflammatory markers, increased free fatty acids, decreased SHBG, hypogonadotropic hypogonadism and subfertility. Mice overexpressing leptin demonstrate early vaginal opening followed by ovarian and uterine maturation, suggestive of accelerated maturation of the HPG axis (19).

Recent studies suggest that early hyperleptinemia related to overnutrition and obesity may be associated with precocious pubertal development (20).

Experiments in female Rhesus monkeys have shown that high calorie intakes results in accelerated body weight and height growth curves. In addition, elevated levels of insulin growth factor 1 (IGF-I) and leptin may signal specifically to GnRH neurons of the HPG axis, and trigger the onset of puberty (21).

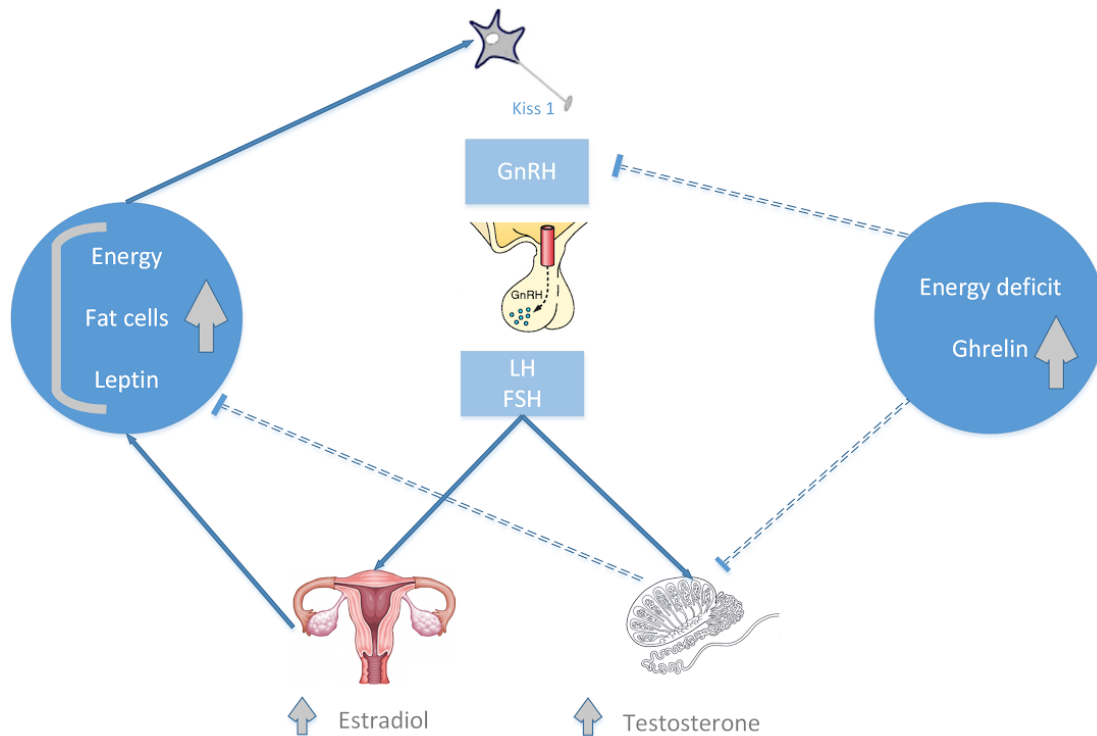


Figure 1. *Leptin stimulates GnRH production through Kiss1 neurons, thus increasing gonadotrophins and sex hormones production. Estrogen promote leptin synthesis, whilst testosterone inhibits leptin production by the adipocytes. Ghrelin increases with energy deficit and inhibits GnRH secretion, thus decreasing gonadotrophins secretion. Ghrelin inhibits testosterone synthesis by testis.*

Besides leptin, ghrelin has emerged as an important peptide orexigenic signal promoting weight gain, which plays a major role in energy homeostasis and the control of body weight (22). Ghrelin levels correlate inversely with BMI. Ghrelin has been shown to have an inhibitory effect on LH secretion in animals and humans. This effect seems to result from an inhibition at a hypothalamic level. Ghrelin effect on FSH secretion is either not well studied or undetectable. Persistently elevated levels of ghrelin as a signal for energy insufficiency, are not only able to inhibit LH secretion but also to impair the normal timing of puberty (22). (see figure 1)

Girls with premature or early thelarche have higher BMI and percent fat than age-matched girls with no thelarche (6) while thelarche occurs earlier in overweight/obese girls. Girls with excessive BMI are more likely to have thelarche between the ages 8.0 and 9.6 years. Early thelarche in obese girls is not the result of GnRH activation, but is rather the isolated consequence of an increased aromatase activity in the adipose tissue where androgens are converted to estrogens. Besides this, obesity is also associated with a decreased hepatic estrogens metabolism (23) and with decreased sex hormone binding globulin (SHBG) levels that increase free estrogen concentrations (24,25).



Figure 2: *Increased adiposity, particularly increased visceral body fat, which can be the result of intrauterine growth retardation, promotes insulin resistance and through actions on the adrenal glands, liver, ovaries and adipose tissue increases sex hormones bioavailability. Increased circulating sex steroids can either have only local effects or also stimulate GnRH and lead to central precocious puberty (Adapted from Ahmed ML et al., Ref 24)*

Increased adiposity in early childhood can predict an earlier onset of puberty: higher BMI z score in girls as young as 36 months of age and higher rate of change of BMI between 36 months old and grade1 (i.e. 6 years old kids) , a period well before the onset of puberty, are associated with earlier puberty (26). There is still a debate and ongoing research to elucidate the nature of the relationship between early rapid weight gain and early puberty. Obesity may trigger early puberty or a common genetic or environmental factor may underlie both phenomena (23, 27).

Pubertal overweight/obese girls have lower frequency and amplitude of LH pulses during sleep, while their responses to GnRH analog are similar to those of non overweight girls. Peak LH responses correlate with LH peak concentrations. In this study, all girls had androgen and estrogen concentrations within normal limits for age (28). This blunted response is possibly related to the slower pubertal tempo reported by some investigators in obese girls. A negative correlation between body fat mass and tempo toward menarche was reported (29).

Age at menarche

Menarche is a significant event for the adolescent and the reproductive life of the woman in general. Several factors influence the age at menarche which can be divided in two groups: genetic and non-genetic. Genetic studies show that the heritability of the age at menarche ranges from 57 to 82 % (30,31,32,33). Early menarche is associated with health problems in adult life. Non-genetic factors are of significant interest, as they can be modified and thus influence the age of menarche. Age at menarche is negatively associated with BMI (34).

Frich and Revell first hypothesized that a critical weight has to be reached for the initiation of menses and that body fat is positively correlated with menarche (1,2). As discussed earlier, the discovery of leptin provided the physiological explanation linking body fat and initiation of menses, since leptin stimulates the pulsatile release of GnRH (35). Kuplowitz et al reported that earlier age at menarche is associated with higher BMI, and that higher parental BMI is associated with earlier menarche (36). Two weight related factors are associated with age at menarche: weight per se and proportion of body fat. Several studies support the evidence that excess weight gain in infancy, childhood, pre puberty and puberty is associated with earlier age at menarche. Other conflicting studies suggest that the distribution of body fat may also have a significant effect on the age at menarche,. Guo and Ji report that higher waist circumferences are strong predictors of earlier menarche and are associated with long-term sequelae (37). Lassek and Gaulin suggest that gluteofemoral fat distribution has the greatest influence on menarche (38). Rapid postnatal weight gain has emerged as another important factor associated with earlier menarche. Earlier weight gain, particularly in small for gestational ages (SGA) babies, strongly predicts a younger age at menarche (39). A recent study in a population of Brazilian students attending private and public

schools, report a higher percentage of overweight/obese girls attending private schools who have menarche at an age earlier than 11 years of age, but not in those attending public schools. In the group of students attending private schools mean age at menarche were 12.3 and 11.6 years respectively in normal weight/underweight and overweight/obese girls. The ages of menarche in the groups of public school students were 12.3 and 12.1 years respectively(40).

Menarche at an early age seems to be directly associated with breast cancer risk and obesity during adulthood (41). A recent study (42) does not replicate previous findings associating early menarche with treatment failure of weight reduction: adolescents and late adolescents had a very high compliance and success rates in weight reduction (> 95%) (42). Efforts towards lifestyle modification aiming at decreasing BMI clearly have to be intensified .

Hyperandrogenemia

Hyperandrogenemia (HA) is present in obese girls starting from prepubertal and early pubertal stages as demonstrated in the elegant work of McCourtney et al (25). Although mechanisms underlying the relationship between peripubertal obesity and HA remain uncertain, these data suggest that differences in insulin and LH contribute to free testosterone (fT) differences between obese and non obese girls (25).

Mean total T was respectively 4.5-fold higher in obese Tanner 1 (prepubertal) girls and 1.6- and 3.3-fold higher in obese Tanner stage 2 and 3 girls than in normal-weight girls. Additionally, mean SHBG was 59–69% lower in the obese Tanner 1, 2, and 3 girls. The combination of high T and low HCG accounts for the estimated 8.8-, 2.2- and 5.8-fold higher mean fT in obese Tanner stages 1, 2, and 3 girls, respectively. All differences reported were statistically significant. Obese girls of all Tanner stages had statistically significant higher concentrations of fasting insulin and insulin sensitivity HOMA index, as compared to normal weight girls. Mean dehydroepiandrosterone sulfate (DHEAS) was higher in obese girls. The difference reached significance in Tanner stage 1 girls only (25).

In prepubertal boys and girls, adrenal androgens increase with adiposity expressed in BMI SDS. In prepubertal children with obesity, DHEAS and androstenedione are increased, as well as free leptin and IGF-I. Children with premature adrenarche have increased BMI. Before the pubertal increase of gonadal steroids, DHEAS concentrations correlate with leptin and BMI, whereas androstenedione concentrations correlate with IGF-I and BMI. Among children with premature adrenarche, neither BMI alone or leptin alone, can explain the precocious adrenal activity (43).

Furthermore some data support the fact that weight loss leads to a decrease of testosterone and DHEAS production in prepubertal girls: testosterone concentrations decreased significantly in obese prepubertal girls losing weight while it did not in those with stable weight. DHEAS concentrations did not change in obese prepubertal girls with substantial and minimal weight loss, whereas it increased in obese prepubertal girls who did not succeed in losing weight (44).

Reinehr et al showed that androgen concentrations correlate with BMI in prepubertal boys: obese boys had increased androgen concentrations as compared to normal weight boys. This difference was not evidenced in pubertal boys (44).

Other studies show that fT concentrations are highly variable among obese prepubertal girls. In a large cohort of peripubertal obese girls morning LH had the greatest ability to predict fT concentrations (45). Similar findings in adolescent with PCOS and hyperandrogenemia leaves us with two possible explanations: LH stimulates androgen production by ovarian theca cells or androgens decrease the gonadostat sensitivity to sex steroid negative feedback, thereby leading to persistently rapid GnRH pulse frequency and increased LH secretion (45, 46). In the same study, insulin concentrations were the second best predictor of fT concentrations. Insulin can intensify LH action at the ovary level and thus stimulate hyperandrogenemia and, through SHBG decrease, increase fT concentrations.(47).

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a common disorder affecting 6-8% of women and characterized by hyperandrogenemia, oligo-anovulatory cycles and polycystic appearance of the ovaries (48,49). PCOS features appear during adolescence or soon after adolescence. The criteria for diagnosis of the syndrome in adolescence are the same as in adults. However physiological variances into puberty during adolescence make it sometimes uneasy to establish. A percentage of normal adolescent girls have anovulation and the ovaries may have polycystic appearance in 50% of normal girls. The HA is of key importance (50). A large percentage of PCOS adolescents and women also present with obesity associated with the stigma of insulin resistance and hyperinsulinemia. (51). The contribution of obesity in the development of PCOS is supported by the relatively frequent development of the syndrome after a significant weight gain (52) and the resolution of the syndrome while maintaining normal weight (53).

The neuroregulatory dysfunction underlying PCOS is an increased GnRH pulses frequency leading to an increased LH pulsatility and a relative FSH deficiency. Persistent rapid GnRH secretions appear to evolve during puberty. Obesity seems to play a significant role in the development of the PCOS which is characterized by endocrine, metabolic and reproductive disorders. Therefore, leptin was hypothesized to be the link between obesity and the development of PCOS. Several studies have tried to clarify the role of leptin but the results are mixed. The inconsistency of the findings may well result from the diversity of the populations studied. Furthermore, in the subset of obese adolescents girls among which 50 % suffer PCOS, hyperleptinemia may play a role (54).

Knusden et al (45) on the basis of the above mentioned data, proposed the following working hypothesis on the obesity-related HA and its potential relationship to the development of PCOS: peripubertal obesity is associated with variable degrees of insulin resistance. Compensatory hyperinsulinemia can then increase ovarian and/or adrenal androgen production and lower SHBG, both of which increase fT concentrations. In susceptible girls, HA lowers the sensitivity of the GnRH pulse generator to negative feedback, leading to persistently rapid GnRH pulses, elevated LH and impaired FSH secretion. These neuroendocrine abnormalities maintain or worsen HA, leading to a vicious cycle underlying the evolution toward the PCOS phenotype (45, 55).

Recent evidence also suggests the existence of an additional vicious circle between abdominal fat deposition and androgen excess leading to PCOS: androgen excess favors the abdominal deposition of fat which in turn promotes androgen secretion by the ovaries and adrenal gland (49). Identifying the primary cause is challenging. The adipose tissue has been proven to be a metabolically active organ which secretes a number of cytokines and adipokines. Adipokines such as leptin and cytokines such as TNF α

and IL-6 are involved in the pathogenesis of obesity-related insulin resistance and have a direct influence on ovarian and adrenal functions. (49). In animal models TNF α induces PCOS features, stimulating rat theca cells proliferation. In vitro studies show that IL-6 induces proliferation of human adrenal cells. Furthermore, visceral adipose tissue expresses enzymes of the adrenal steroidogenesis cascade, such as 3 β hydroxysteroid dehydrogenase, 17 β hydroxysteroid dehydrogenase, aromatase and type 11-1 β hydroxysteroid dehydrogenase and might in this way contribute to or modulate HA in PCOS. While HA is usually the result of obesity and insulin resistance, it has been shown that long term testosterone administration is associated with increased visceral fat. Prenatal exposure to increased androgen concentrations leads to phenotypic characteristics of PCOS in non-human primate, ovine and rodent animal models. As a consequence, prenatal exposure of human female embryos to increased androgen concentrations may correlate with increased visceral adiposity and insulin resistance in late adolescence and adulthood (54,56).

Ovarian theca cells from PCOS patients appear to have the intrinsic property of synthesizing excessive amounts of androgens when exposed to appropriate stimuli (57) which could partly be of genetic origin (58). Leptin does not appear to play a central role in HPG dysfunction and hyperandrogenemia. Previous studies have shown the lack of correlation between leptin and LH, T, DHEAS and estradiol concentrations (59, 60). However, some other data support a positive correlation between leptin and LH concentrations in PCOS subjects and controls (61). Notably, there is evidence that the effect of leptin in the kiss1 neurons depends on the duration of hyperleptinemia. Thus, very early hyperleptinemia stimulates kiss1 neurons while prolonged hyperleptinemia suppresses kiss1 neurons and this can be related to anovulation as part of the PCOS (56). These findings illustrate that the effects of increased leptin concentrations on the HPG axis and more specifically on the Kiss 1 system might depend on the timing, the duration and the degree of this elevation (51).

Leptin concentrations correlate negatively with concentrations of SHBG and free sex steroids (62, 63) but this correlation may be mediated by insulin resistance. Hyperleptinemia may play a role in the development of PCO syndrome at the level of the ovaries. Leptin receptors are present in the granulosa and theca cells of human ovarian follicles. Low leptin concentrations stimulate estrogen and progesterone production by the theca cells, whilst high concentrations inhibit their production, as shown by in vitro studies (64). However, in women with PCOS, no differences were detected in leptin concentrations, among the subjects with or without anovulatory cycles, implying that the role of leptin in follicular maturation is mediated through a difference in sensitivity (65).

Obesity and insulin resistance may not be the cause of PCOS as lean adolescents and women may suffer PCOS. Obesity and insulin resistance are more likely to amplify rather than cause the reproductive features of PCOS (66). Insulin sensitizers, like metformin used in the treatment of PCOS, decrease insulin but not leptin concentrations, underlining the complex pathophysiology of this syndrome (67).

Reproduction

The complex metabolic regulation of reproduction centers on the KISS1 neurons. They receive messages from leptin, ghrelin, neuropeptide Y (NPY), melanocortin, insulin and insulin like growth factor (17). Women who are obese are more likely to have fertility problems (68). Thus, many fertilization programs

exclude severely obese women, as they have lower success rate and increased complication risk level (69).

Obesity in late adolescence and early adulthood predicts lower fertility rates, as women who are obese at 17-24 years of age are less likely to be mothering 1-2 children at 45 years of age (69). Obese women have lower fertility rates. Even in the absence of PCOS, women with BMI higher than 25 kg/m² have longer follicular phases, shorter luteal phases, lower FSH, LH, and progesterone levels (70). Impaired oocyte function and diminished endometrial receptivity aggravate the subfertility issue (70).

Boys

Most of the evidence presented above applies to obese girls. A recent longitudinal population based study reported that a higher BMI during childhood increases the possibility for delayed puberty among boys. Boys with increased fat mass do not have earlier puberty in contrast to what happens in girls (8). The pathophysiological mechanism has not been completely elucidated. Data concerning sex hormone levels and pubertal transition for boys are scarce. Prepubertal and pubertal obese boys have lower SHBG than normal weight boys, but testosterone levels do not differ. Pubertal obese boys have a higher estrogen/testosterone ratio than normal weight boys. In the prepubertal boys, SHBG concentrations are negatively correlated with testosterone concentrations and positively with the estradiol/testosterone ratio. Increased estrogen concentrations inhibit GnRH secretion while leptin resistance may contribute to lower gonadotropin concentrations.

Obese men have decreased testosterone and gonadotropin levels and increased estrogen levels (71). As a result of increased peripheral conversion they have increased estrogen concentrations which are related to erectile dysfunction through an increased negative feedback from the estrogen and a subsequent hypogonadotrophic state (70). Additionally, impaired spermatogenesis and poor quality and sperm motility have been reported in obese men (70). Inhibin-B concentrations have been found to be lower in obese young adult men compared with normal-weight men but not in prepubertal boys. A current hypothesis is that the negative impact of obesity on Sertoli cells proliferation during (peri)puberty may contribute to male reproductive dysfunction in adulthood (72). Several studies clearly show that obese men have an increased risk of subfertility and subfecundity, mainly due to the abnormal regulation of the HPG axis. The connecting link is again leptin: reduced leptin signaling leads to reduced GnRH neuronal activity. Increased leptin resistance associated with obesity also results in altered concentrations of reproductive hormones and may explain the association between BMI, altered semen parameters and infertility (73) (Fig 3.). Whether the mechanisms identified in adult men are applicable to prepubertal and peripubertal boys needs further clarification.

Conclusions

Obesity and increased adiposity, particularly central adiposity, mediates alterations in leptin and insulin secretion and sensitivity, thus interfering at different levels in the process of pubertal development and reproductive function. The main outcomes are prepubertal HA in girls and boys, a trend towards an earlier thelarche, puberty and menarche in girls but a slower pubertal progression in boys. Obesity increases the risk of PCOS development among adolescent girls. Finally, obesity has an impact in a number of

reproductive targets, including the HPO axis, oocyte quality, endometrial receptivity in women and spermatogenesis in men.

References

1. Frisch RE. The right weight: body fat, menarche and fertility. *Proc Nutr Soc.* 1994; 53:113–129.
2. Frisch RE and Revelle R. Height and weight at menarche and a hypothesis of menarche. *Archives of Disease in Childhood,* 1971; 46: 695–701.
3. Johnston FE, Roche AF, Schell LM, et al. Critical weight at menarche. Critique of a hypothesis. *Am J of Diseases of Children,* 1975; 129:19–23.
4. Crawford JD, C.Osler DC., Body composition at menarche: the Frisch Revelle hypothesis revisited. *Pediatrics,* 1975;56 (3):449–458..
5. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics* 2008;121(Suppl 3):S172–191.
6. Kaplowitz PB, Slora E, Wasserman RC, et al. Earlier onset of puberty in girls: Relation to increased Body Mass Index and race. *Pediatrics* 2001; 108(2) 347-353.
7. Franks S. Polycystic ovary syndrome in adolescents. *Int J Obes (Lond)* 2008;32:1035–1041.
8. Lee JM, Kaciroti N, Appugliese D et al. Body mass index and timing of pubertal initiation in boys *Arch Pediatr Adolesc Med* 2010; 164(2) 139-44
9. Burt Solorzano CM and McCartney CR. Obesity and the pubertal transition in boys and girls *Reproduction.* 2010; 140(3): 399–410.
10. Sanchez-Garrido MA, Tena-Sempere M. Metabolic control of puberty: roles of leptin and kisspeptins. *Hormones and Behavior* 2013; 64:187–194.
11. Garcia-Mayor RV, Andrade MA, Rios M, et al. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary–gonadal hormones and pubertal stage. *J Clin Endocrinol Metab*1997; 82:2849–2855.
12. Mantzoros CS, Flier JS & Rogol AD. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. Rising leptin levels may signal the onset of puberty. *J Clin Endocrinol Metab* 1997;82:1066–1070.
13. Rosenbaum M, Leibel RL. Clinical review 107: role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. *J Clin Endocrinol Metab* 1999; 84: 1784–1789.
14. Farooqi IS, Matarese G, Lord GM et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 2002; 110:1093–1103.
15. Quenell JH, Mulligan AC, Tups A, et al. Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. *Endocrinology* 2009;150:2805–2812.
16. Navarro VM, Ruiz-Pino F, Sanchez-Garrido MA et al. Role of neurokinin B in the control of female puberty and its modulation by metabolic status. *J of Neuroscience* 2012;32:2388–97..
17. Pinilla L, Aguilar E, Dieguez C, et al. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. *Physiological Reviews* 2012; 92: 1235–316.
18. Moon HS, Dalamaga M, Kim SY et al. Leptin’s role in lipodystrophic and non lipodystrophic insulin-resistant and diabetic individuals. *Endocrine Reviews* 2013; 34:377–412.
19. Yura S, Ogawa Y, Sagawa N, et al. Accelerated puberty and late-onset hypothalamic hypogonadism in female transgenic skinny mice overexpressing leptin. *J Clin Invest* 2000;105:749–755.

20. Elias CF, Purohit D. Leptin signaling and circuits in puberty and fertility *Cell. Mol. Life Sci.* 2013; 70:841–862.
21. Terasawa E, Kurian JR, Keen KL, et al. Body weight impact on puberty: effects of high-calorie diet on puberty onset in female Rhesus monkeys. *Endocrinology* 2012;153: 1696–1705.
22. Tena-Sempere M. Ghrelin, the gonadal axis and the onset of puberty. *Endocr Dev.* 2013; 25: 69-82.
23. Jasik CB, Lustig RH. Adolescent obesity and puberty: the “perfect storm”. *Annals of the New York Academy of Sciences* 2008;1135: 265–279.
24. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. *Trends Endocrinol Metab* 2009; 20: 237–242.
25. McCartney CR, Blank SK, Prendergast KA, et al. Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre- and early pubertal obese girls. *J Clin Endocrinol Metab.* 2007; 92:430–6.
26. Lee JM, Appugliese D, Kaciroti N, et al. Weight status in young girls and the onset of puberty. *Pediatrics* 2007;119: e624–630.
27. DiVall SA, Radovick S. . Endocrinology of female puberty. *Curr Opin Endocrinol Diabetes Obes.* 2009; 16:1-4.
28. Bordini B, Littlejohn E, Rosenfield RL. Blunted sleep-related luteinizing hormone rise in healthy premenarcheal pubertal girls with elevated body mass index. *J Clin Endocrinol Metab* 2009; 94:1168–1175.
29. de Ridder CM, Thijssen JH, Bruning PF, et al. Body fat mass, body fat distribution, and pubertal development: a longitudinal study of physical and hormonal sexual maturation of girls. *J Clin Endocrinol Metab* 1992; 75:442–446.
30. Yermanchenko A., Dvornyk V.. Nongenetic determinants of age at menarche: a systematic review. [Biomed Res Int.](#) 2014;2014:371583. doi: 10.1155/2014/371583. Epub 2014 Jun 23.
31. Anderson C. A., Duffy D. L., Martin N. G., and al. Estimation of variance components for age at menarche in twin families. *Behavior Genetics*, 2007; 37(5): 668–677.
32. Kaprio J, Rimpel A., Winter T., et al. Common genetic influences on BMI and age at menarche. *Human Biology*, 1995; 67 (5):739–753,
33. Morris D.H., Jones M.E., Schoemaker M.J., et al. Familial concordance for age at menarche: analyses from the breakthrough generations study. *Paediatric and Perinatal Epidemiology.* 2011; 25 (3) 306–311.
34. Freedman DS, Khan LK, Serdula MK, et al. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics* 2002;110:e43.
35. Von Schnurbein J., Moss A., Nagel S.A. et al. Leptin substitution results in the induction of menstrual cycles in an adolescent with leptin deficiency and hypogonadotropic hypogonadism, *Horm Res in Paediatrics*, 2012;77(2):127–133.
36. Kaplowitz P.. Pubertal development in girls: secular trends. *Current Opinion in Obstetrics and Gynaecology* 2006;18:487–491.
37. Guo X., Ji C., Earlier menarche can be an indicator of more body fat: study of sexual development and waist circumference in Chinese girls,” *Biomedical and Environmental Sciences*, 2011; 24 (5):451–458.
38. Lassek W. D, Gaulin S. J. C., “Brief communication: menarche is related to fat distribution,” *Am J Phys Anthropol*, 2007;133(4):1147–1151.

39. Ong K., Emmett P., Northstone K. et al., Infancy weight gain predicts childhood body fat and age at menarche in girls. *J Clin Endocrinol and Metab*, 2009;94(5):527–1532.
40. Castillo S. D, Nucci L.B. Age at menarche in schoolgirls with and without excess weight.. *J Pediatr (Rio J)*.2015;91:75-80.
41. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: Associations and interactions in an international case-control study. *Int J Cancer* 1990; 46(5): 796–800.
42. Cuzmar I, Cortes E, Rizo M. Age group menarche and regularity of menstrual cycles as efficiency predictors in the treatment of overweight. *Nutr Hosp*. 2015;31:637-641.
43. l' Allemand D., Schmidt S.,Rousson V. et al. Associations between body mass, leptin, IGF-I and circulating adrenal androgens in children with obesity and premature adrenarche. *Eur J of Endocrinology* 2002; 146: 537–543
44. Reinehr T., de Sousa G., Roth CL., et al. Androgens before and after weight loss in obese children. *J Clin Endocrinol Metab* 2005; 90(10):5588–95.
45. Knudsen K.L.Blank S.K., Burt Solorzano C., et al. Hyperandrogenemia in obese peripubertal girls: correlates and potential etiological determinants. *Obesity (Silver Spring)*.2010;18:2118–24.
46. Chabra S., McCartney CR., Yoo RY. et al. Progesterone inhibition of the hypothalamic gonadotropin-releasing hormone pulse generator: evidence for varied effects in hyperandrogenemic adolescent girls. *J Clin Endocrinol Metab* 2005;90:2810–2815.
47. Dunkel L., Sorva R., Voutilainen R. Low levels of sex hormone-binding globulin in obese children. *J Pediatr* 1985; 107:95–97
48. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004; 81:19–25.
49. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006; 91:4237–45.
50. Mortensen M, Rosenfield RL., Littlejohn E. Functional significance of polycystic-size ovaries in healthy adolescents. *J Clin Endocrinol Metab*. 2006; 91:3786–90.
51. Vazquez MJ., Romero-Ruiz A., Tena-Sempere M. Roles of leptin in reproduction pregnancy and polycystic ovary syndrome: consensus knowledge and recent developments. *Metabolism Clinical and Experimental*. 2015; 64: 79-91
52. Gambineri A., Pelusi C., Vicennati V. et al. Obesity and the polycystic ovary syndrome. *Int. J. Obes. Relat. Metab. Disord*. 2002; 26: 883–896.
53. Escobar-Morreale H.F., Botella-Carretero JL., Alvarez-Blasco F. et al. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J. Clin. Endocrinol. Metab*. 2005; 90: 6364–6369.
54. Escobar-Morreale H.F, San Millan J.L. Abdominal adiposity and the polycystic ovary syndrome. *Trends Endocrinol Metab* 2007;18:266–72.
55. Burt Solorzano CM., McCartney CR., Blank SK., et al. Hyperandrogenemia in adolescent girls: origins of abnormal gonadotropin-releasing hormone secretion. *BJOG*. 2010; 117(2): 143-149.

56. Castellano JM., Bentsen AH., Sanchez-Garrido MA., et al. Early metabolic programming of puberty onset: Impact of changes in postnatal feeding and rearing conditions on the timing of puberty and development of the hypothalamic Kisspeptin system. *Endocrinology* 2011;152:3396–408.
57. Wickenheisser JK., Nelson -DeGrave VL., McAllister JM.. Human ovarian theca cells in culture. *Trends Endocrinol. Metab.* 2006;17: 65-71.
58. Escobar-Morreale HF, Luque-Ramirez M, San Milan JL. The molecular-genetic basis of functional hyperandrogenism and the polycystic ovary syndrome. *Endocr. Rev.* 2005; 26: 251–282.
59. Mantzoros CS, Dunaif A, Flier JS. Leptin concentrations in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1997;Jun;82(6):1687-91.
60. 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):509-15
61. Chen X., Jia X., Qiao J., et al. Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome. *J Mol Endocrinol* 2013:R21–37.
62. Laughlin GA., Morales AJ., Yen SS.. 1997 Serum leptin levels in women with polycystic ovary syndrome: the role of insulin resistance hyperinsulinemia. *J Clin Endocrinol Metab* 1997; 82: 1692–1696.
63. Hahn S., Haselhorst U., Quadbeck B. et al. Decreased soluble leptin receptor levels in women with polycystic ovary syndrome. *Eur J Endocrinol* 2006; 154: 287–294.
64. 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. *J Endocrinol Invest* 2009; 32: 415–419.
65. Carmina E, Bucchieri S, Mansueto P, et al. Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome. *Fertility and Sterility* 2009; 91: 1332–1335.
66. Walters KA., Allan CM., Handelsman DJ. Rodent models for human polycystic ovary syndrome. *Biological Reproduction* 2012;149: 1–12.
67. Tfayli H, Ulnach JW, Lee S, et al. Drospirenone/ethinyl estradiol versus rosiglitazone treatment in overweight adolescents with polycystic ovary syndrome: comparison of metabolic, hormonal, and cardiovascular risk factors. *J Clin Endocrinol Metab* 2011; 96:1311–1319.
68. Brannian JD. Obesity and fertility. *S D Med* 2011;64(7):251-254.
69. Jokela M, Elovainio M, Kivimaki M.. Lower fertility associated with obesity and underweight: the US National Longitudinal Survey of Youth. *Am J Clin Nutr* 2008; 88(4): 886-893.
70. Klenov V.E., Jungheim E. Obesity and reproductive function: a review of the evidence. *Curr Opin Obstet Gynecol.* 2014, 26:455–460.
71. Hammoud AO., Meikle AW., Reis LO., et al. Obesity and male infertility: a practical approach. *Semin Reprod Med* 2012; 30:486–495.
72. Michalakis K., Mintziori G, Kaprara A. et al. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. *Metabolism Clinical and Experimental.* 2013; 62: 457-78.
73. Landry D, Cloutier F., Martin LJ. Implications of leptin in neuroendocrine regulation of male reproduction *Reproductive biology* 2013; 13: 1-14.

~ About the Authors ~

Elpis-Athina Vlachopapadopoulou



Dr. Elpis-Athina Vlachopapadopoulou, received the MD degree from the University of Athens, Greece with “magna cum laude” in 1986. Following completion of Pediatric Residency at St. Luke’s/Roosevelt Hospital Center of the Columbia College of Physicians and Surgeons campus (1990) she proceeded to a Pediatric Endocrinology Fellowship at New York Hospital- Cornell Medical Center in NYC (1990-94). She became Board Certified in both Pediatrics 1990 and Pediatric Endocrinology, 1997. She returned to Athens, Greece in 1994, and she is working in Children’s Hospital “P. & A. Kyriakou”, Dept. of Growth and Development-Endocrinology since 1997, currently as Director. She holds Greek Boards in Pediatrics and also Endocrinology.

Dr Vlachopapadopoulou is a member of the Endocrine Society since 1994, of the European Society of Pediatric Endocrinology since 1997 and of the European Society of Endocrinology since 2006. She is actively participating in International meetings with more than 100 presentations, as well as, several in Greek symposia and meetings. Her main research interests focus on growth disorders, growth hormone deficiency, precocious puberty, obesity and long-term endocrine sequelae following treatment for childhood malignancies and bone marrow transplantation. She has authored 30 publications in peer-reviewed international and Greek journals, as well as book chapters. She has been a reviewer for journals, ESPE and ECOG meetings, as well as, national journals and meetings. She is the principal investigator in three Phase –II international protocols and co-investigator in four international observational studies.

She is very active in the field of childhood obesity. Since 2003, has been a member of the European Childhood Obesity Group. She follows and offers treatment plan to more than 600/year overweight–obese children. She is leading investigator for the Hellenic National ActionPlan for the Assessment Prevention and Treatment for Childhood Obesity in Greece with important research and field interventions among children and adolescents relating to obesity in Greece.

~ How To Use This article ~

You are **free to use, share and copy this content** by quoting this article as follow:

Vlachopapadopoulou E (2015). Childhood obesity: Implications In Pubertal Process. In M.L. Frelut (Ed.), The ECOG's eBook on Child and Adolescent Obesity. Retrieved from ebook.ecog-obesity.eu

Also make sure to **give appropriate credit** when using this content. Please visit ebook.ecog-obesity.eu/terms-use/summary/ for more information.

~ Final Word ~

Thank you for reading this article.

If you have found this article valuable, please share it with someone that will be interested in.

Also make sure to visit ebook.ecog-obesity.eu to read and download more childhood obesity-related articles.