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Review

Early onset adiposity: A pathway to polycystic ovary syndrome in adolescents?

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ABSTRACT

Polycystic Ovary Syndrome is a heterogenous syndrome of unknown causation commonly associated with obesity. The particular timing of the onset of obesity may be important, since the earlier the onset of obesity the greater the severity of the metabolic and hormonal aberrations. Early postnatal life and peripubertal periods may be critical windows for the development of the "adiposity insult". The interaction of adiposity with genetic traits as well as with prenatal environmental factors may further aggravate the metabolic and endocrine abnormalities, which become more pronounced in adolescence.

Key words: Adolescence, Intrauterine growth retardation, Obesity, PCOS, Visceral adiposity

INTRODUCTION

Polycystic Ovary Syndrome (PCOS), the most common endocrine disorder of women of reproductive age,[1] is characterized by chronic anovulation and clinical or biochemical hyperandrogenemia.[2] The pathogenesis of PCOS remains largely unknown. Ongoing research points to a multifactorial pathophysiologic model[3] interweaving genetic[4] and environmental/nutritional factors.[5] Recently, the ESHRE/ASRM Consensus[6] has introduced new phenotypes of PCOS requiring two of the following features for the diagnosis of PCOS: chronic anovulation, biochemical and/ or clinical hyperandrogenemia and distinct sonographic appearance of the ovaries. The actual clinical significance of these phenotypes is controversial[7] and the AES position statement did not declare the inclusion of anovulatory non-hyperandrogenic women with ultrasonographic polycystic ovarian morphology in the PCOS cohort.[7] Although not included in the definition of PCOS, research has placed particular emphasis on the pivotal pathogenetic role of adiposity in PCOS. Relevant literature has eloquently suggested that adiposity and the attendant insulin resistance (IR) can significantly contribute to hormonal aberrations[8,9] and amplify the metabolic[10-13] and cardiovascular risk,[14-16] which may be inherently increased in PCOS. The detrimental consequences of adiposity appear to originate from its clinical emergence onwards and may already be present in adolescence.[17] Given the alarming spread of the

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"obesity epidemic" in childhood and adolescence,[18] this review attempts to provide insights into the role of early adiposity in the pathogenesis of PCOS in adolescents.

Obesity in childhood and adolescence is intimately linked with IR[28] and has emerged as a significant initiator of early onset Metabolic Syndrome.[18] Visceral adiposity appears to be of major pathophysiologic relevance to insulin resistance and Metabolic Syndrome.[29,30] Pertinent studies have shown that IR is associated with increased prevalence of MBS among overweight or obese Hispanic adolescents,[31,32] pointing to the key role played by obesity and obesity-related IR in the pathogenesis of the MBS.[30]

Visceral adiposity is the commonest phenotype of PCOS, present in 50–70% of adult patients,[17,33] and the same appears to hold true among adolescents with hyperandrogenemia.[25] This devastating incidence has prompted investigators to explore the pathophysiologic implications of obesity in the pathogenesis or clinical emergence of PCOS.

Peripubertal obesity has been incriminated for peripubertal hyperandrogenemia and the consequent endocrine/reproductive disturbances in adult women.[34,35] In the study by Mc Cartney et al, overweight girls (defined as BMI-for-age ≥95th percentile) presented with significant hyperandrogenemia compared to their normal-weight peers,[34] findings indicating that obesity plays an inciting role in the early development of androgen excess, which may precipitate PCOS.

The well recognized role of adipose tissue as an additional site of testosterone formation from circulating precursors may account in part for the adverse effects of adiposity on the hormonal profile.[36,37]

Additionally, obesity is intimately linked with insulin resistance and compensatory hyperinsulinemia and the latter is postulated to have a multifactorial impact on the ovarian function. Hyperinsulinemia may directly stimulate ovarian theca cell androgen synthesis[38,39] and synergise with LH in premature follicular luteinization. Hyperinsulinemia also suppresses hepatic production of SHBG, further increasing the unbound testosterone concentrations.[38] By contrast, weight loss[40,41] and pharmaceutical modalities that ameliorate hyperinsulinemia were shown to be beneficial to the alleviation of hyperandrogenemia and ovulatory dysfunction in these individuals.[42,43,91]

Hyperandrogenemia of peripubertal obesity may aggravate the PCOS phenotype in a dual mode. In adult women with PCOS[44] and in hyperandrogenemic adolescents,[45-48] androgen excess has been associated with persistently increased GnRH pulse frequency, which has been attributed to the androgen-induced resistance of the GnRH pulse generator to negative progesterone feedback.[49-52] This abnormality could result in unduly elevated LH secretion, which may perpetuate ovarian androgen production and ovulatory dysfunction, contributing to the adult PCOS phenotype.

Additionally, peripubertal hyperandrogenemia in conjunction with obesity may precipitate significant metabolic aberrations emerging in such an early stage and lasting throughout the individual's lifetime. The postulated relationship between adiposity and androgen excess appears to be bidirectional. Early adiposity promotes hyperandrogenemia, and conversely androgen excess may conspire to central adiposity and PCOS related metabolic aberrations (Figure 1).[35,53] Hyperandrogenemia may impose an independent burden of metabolic derangement which adds to the

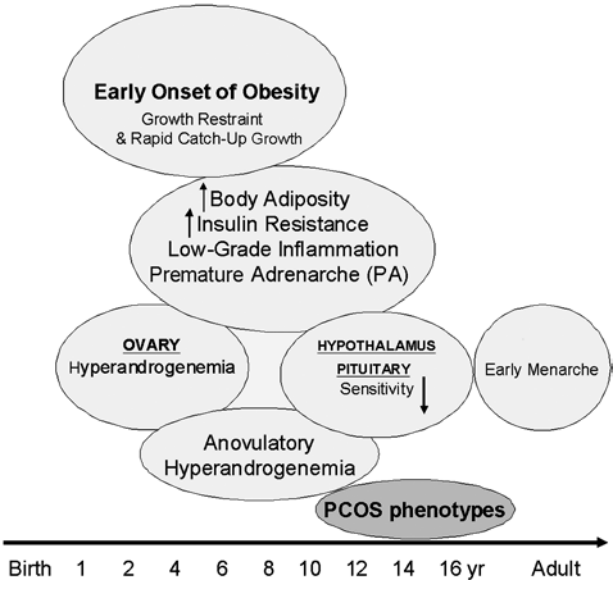

Figure 1. Early onset of obesity and hyperinsulinemia effect on peripubertal hyperandrogenemia.

obesity related metabolic risk. Specifically, hyperandrogenemia appears to contribute to the characteristic body fat distribution linked with IR and MBS.[53] The validity of this concept was initially shown in adult patients and presumably also applies to adolescent girls with PCOS (or hyperandrogenemia).

Recent retrospective studies in adult women with PCOS have suggested that the prevalence of MBS is twice that of the general population independently of Body Mass Index[54,55] and adolescents with PCOS are reasonably considered to run a proportionally heightened risk for metabolic aberrations[56-58] or the full-blown Metabolic Syndrome.[25]

The study by Coviello et al[25] provided strong evidence that adolescents with PCOS have an increased prevalence of MBS and pointed to hyperandrogenemia as a risk factor for MBS, independently of obesity and IR.

Corroborating data have been derived from studies among PCOS subjects showing the beneficial metabolic effect elicited by antiandrogen therapy. Flutamide, a non-steroidal antiandrogen, has been shown to decrease the central fat mass when assigned as monotherapy in obese and non-obese adult patients[59] as well as when co-administered with metformin in adolescents with PCOS.[60,61] Ibanez et al have also provided evidence of an additive effect on the improvement of body composition, androgen levels, lipid levels and IR when metformin and flutamide were combined[61], probably reflecting an interwoven circuit between hyperandrogenemia, hyperinsulinemia and obesity in the pathogenesis of the PCOS.

The putative contribution of androgen excess to the development of the MBS (the metabolic component/equivalent of PCOS) is further supported by the identification of androgen receptors (ARs) on preadipocytes and adipocytes. The AR expression is significantly more pronounced in the visceral vs the subcutaneous fat, suggesting the preferential visceral fat accumulation in the setting of hyperandrogenemia.[62]

Moreover, adipose tissue is a known source of proinflammatory cytokines such as TNF-α, IL-6 and plasminogen activator inhibitor, which have been found to be increased in individuals with MBS.[63] Thus, hyperandrogenemia may exert adverse effects on adipose tissue metabolism by modifying the production or action of cytokines.[35]

The above presented model reconciles existing data on the role of early adiposity in the development of metabolic and hormonal aberrations of PCOS. Adiposity of childhood and adolescence appear to superimpose an additional risk upon an inherent predisposition rather than being a primary determinant. This putative inherent proneness may be conferred both by genetic traits[4,64-66] and by environmental cues acting from fetal life onwards.[5,65,67] The developmental cascade interweaves several interacting factors with each other to orchestrate the final outcome, namely the hormonal and reproductive aspects of PCOS. In light of this, early adiposity has been suggested as contributing to peripubertal hyperandrogenemia, which may act as a trigger of reprogramming adaptations of the hypothalamic-pituitary axis.[35]

We will further discuss the relevance of low birth weight and early catch-up growth on the model of early adiposity and the implications for the development of PCOS.

A putative developmental program linking low birth weight (LBW) and early catch-up weight gain with hyperandrogenemia in early adolescence and the metabolic and hormonal stigmata of PCOS in late adolescence and adulthood has been suggested. This process has also been associated with the propensity to develop several components of MBS, such as central obesity, IR and impaired glucose tolerance.[68-70]

Early weight gain appears to be a “key player” in the putative chain of causality between LBW and metabolic/endocrine derangements. The exact timing of the catch-up of weight, which may be of significant relevance to the adiposity-related impact, continues to be debated.[71] Several contemporary birth cohort studies have shown that early infant weight gain is positively associated with subsequent obesity risks.[72,73] In 1-year old infants who were born small for gestational age (SGA) and experienced a rapid catch-up of weight,[74] insulin sensitivity was found to be reduced with a trend for further aggravation.[75,76]

Other studies of adults with cardiovascular disease and Type 2 Diabetes have demonstrated that

weight gain during early childhood, but after infancy, contributes to persistent obesity in adulthood.[77,78] In another study, both infancy and early childhood body weights contributed independently to increased body fat mass at age 17 years.[79]

However, the first study to report longitudinal data on the development of total and central body fat mass and the metabolic parameters in SGA children with spontaneous postnatal catch-up weight gain was performed by Ibanez et al.[79] In this study, SGA children were shown to gain more body fat and abdominal fat mass than appropriate for gestational age (AGA) children, along with a change from insulin sensitivity to insulin resistance between ages 2 to 4 years. These striking differences occurred despite comparable BMI values in SGA and AGA children. Moreover, in 4-year old children, total and abdominal fat mass were shown to correlate with weight gain in the age range of 0-2 years, pointing to the major role of early postnatal increments of weight in precipitating future obesity.[79]

In this context, insulin resistance has emerged as the core abnormality.[79] A mechanism of muscle specific IR has been purported to operate in SGA infants with early catch-up growth and lead to lesser gains in lean mass and the diversion of nutrients toward fat accumulation.[80] The accumulation of visceral fat may lead to insulin resistance, by increasing the release of FFAs, while the early development of hyperinsulinemia could provide positive feedback to promote peripheral and central fat deposition.

Beyond the metabolic defects mimicking the PCOS metabolic component, low birth weight has also been associated with the endocrine aberrations of PCOS.[81-88]

SGA infants with early catch-up growth have shown a predisposition to premature adrenarche, a potential forerunner of ovarian hyperandrogenism in adolescence and adulthood.[81] Longitudinal and cross-sectional studies have shown that girls with premature pubarche and a history of low birth weight (LBW-PP girls) are at risk for early menarche and further progression to hyperinsulinemic hyperandrogenism and anovulation.[81-88]

Furthermore, premature androgen excess may represent an additional mechanism, besides early insulin resistance, that contributes to the elevated metabolic risk of individuals with a history of low birth weight. Girls with a history of LBW have been tentatively identified as showing a cluster of cardiovascular risk factors at the age of 8 years.[82,83]

Insulin resistance and hyperinsulinemia may be the key mechanism underlying this perpetual sequence of hormonal and metabolic aberrations. This sequence may commence early in life and extend throughout life (Figure 2). An attempt to optimize the outcome of girls at risk for PCOS by reversing their metabolic abnormalities has been undertaken by Ibanez et al. The investigators have administered metformin in pre- or peripubertal hyperandrogenic girls with a history of low birth weight and premature pubarche and have found significant improvement across a wide array of hormonal and metabolic abnormalities.[89-92] The attenuation of hyperandrogenemia and menstrual disturbances that was accomplished in concert with the improvement of insulin sensitivity has attested to the causal role of insulin resistance in this pathogenic circuit.

On the whole, rapid postnatal weight gain and adiposity appear to dominate over the initial prenatal triggering event, namely fetal growth restriction and low birth weight. It could be suggested that the initial impact of a triggering event might be relatively subtle and the permanent reflections of this event may be magnified by environmental insults through

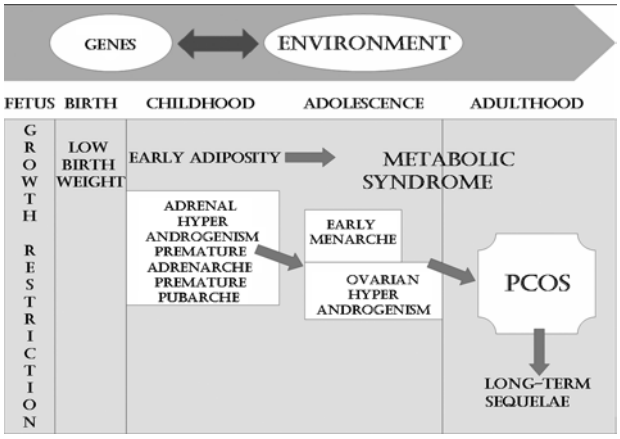

Figure 2. The hypothetical natural course of PCOS from birth to adulthood.

time. In the particular context of low birth weight and early catch-up, the mismatch between prenatal and postnatal environment may create a favourable ground for metabolic and endocrine aberrations to develop. Sustaining the ideal body weight in the postnatal period and throughout the life cycle could counterbalance the predisposition of individuals with LBW to the aforementioned morbidities.

CONCLUSIONS

Early female adiposity is increasingly recognized as a critical cue for the development or the aggravation of clinical manifestations of PCOS. This has highlighted the prime importance of timely intervention in the clinical course of obesity to minimize the associated hormonal and metabolic aberrations. However, not all obese/overweight adolescents share a similar risk for developing these abnormalities. Genetic predisposition, duration of obesity, presence of other adverse factors from the medical history (like the history of low birth weight) are major determinants of risk for PCOS and the associated hormonal and metabolic abnormalities. The appropriate risk stratification for adolescents could guide clinicians in recognizing overweight youth who are at higher risk and thereby lead to a prompt intervention before consequences become apparent and probably irreversible.

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