LETTER TO EDITOR

Adolescent PCO – The Modern Approach

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Introduction:

The incidence of polycystic ovary (PCO) in adolescence is increasing day by day, and the most important causative factor is abnormal lifestyle. PCO arises from increase in male hormone attack on the females, and abnormal lifestyle is responsible for this. The fact is that PCO is basically a misnomer. There is no presence of cyst in the ovaries. The immature and arrested follicles are called cysts. Look of the ovary is not a concern, as PCO is a functional endocrinal problem. In reality, the parents are worried because of the look, weight-gain and irregularity of period of adolescent girls. The problem of self image and fat maleish look of the girl becomes a concern. Moreover, comments from neighbors and associates and wrong advice by medical personnel cause more problems in the matter.

Natural History of PCOS:

The natural history of PCO is also interesting. About 30% of the women are pre-determined to develop PCO genetically, as it is a polygenic disorder. The ovaries look PCO in ultrasound and also in naked eyes. About 10% of them develop signs and symptoms of PCO due to stress, obesity and abnormal lifestyle. Rest 20% though having morphological PCO, remain clinically unnoticed. If weight loss, stress control and lifestyle management can be ensured, these 10% women can go back to the clinically unnoticed group.

Factors causing PCOS:

The precipitating factors of PCO are primarily due to genetic background. The enigmatic multidisciplinary genetic disorder both due to X-linked & autosomal genes are responsible here, and this is represented by a strong family history. The psychological stress, obesity and weight gain trigger the development of clinical features of polycystic ovarian syndrome (PCOS), and these might act as environmental factors, which might have genetic basis too. Premature puberty may be a result of PCOS, so also intra-uterine androgen exposure due to chemicals like Endocrine Disrupting Chemicals (EDCs) or virilising hormones. There is an interesting issue that normal pubertal metabolic changes may mimic PCOS, but they disappear after the onset of puberty. In many cases, these features may persist, giving rise to frank PCOS due to persistent hyper-insulinaemia.

Diagnosis of PCOS:

According to Rotterdam consensus 2004, [1, 2] any two of the following three features are diagnostic of PCOS –

1. Chronic oligo or anovulation for more than 6 months
2. Clinical and biochemical evidence of hyperandrogenism
3. PCO on ultrasound

It is interesting that in adolescence, PCOS may be under or over-diagnosed, as the metabolic or ovarian changes are similar both in cases and normal adolescent girls. The multiple antral follicles in peri-pubertal ovary may be misunderstood as PCO. Certain symptom in adolescence may be over-diagnosed as PCO. The diagnosis is usually achieved by USG features of ovarian

androgen profile, serum insulin level, DHEA, prolactin and cortisol estimation, which may help as excluding criteria.

The importance of diagnosing PCO in adolescence is to prevent recent and remote problems. The recent problems include hirsuitism, psychological problems, abnormal menstrual cycle, some degree of depression, and abnormal self-esteem. The remote problems may be divided into biochemical, health and reproductive issues. The remote biochemical problems may be DM-T2, hyper-lipidaemia, hyper-insulinaemia and hyper-androgenism. The health issues may be CHD, DM-T2, hyper-tension and endometrial carcinoma. The reproductive issues may be infertility, recurrent spontaneous abortion (RSA), GDM, PIH, premature labor and endometriosis.

Clinical Presentation of PCOS:

The clinical presentation of PCOS is irregular menstrual cycles, which are less than 6 cycles per year. Obesity, hirsutism, acne, alopecia and acanthosis nigricans are also other important manifestations of PCOS. Hyper-androgenism and hyper-insulinism [3] are some basic hormonal defects, also giving rise to PCOS.

Hyper-insulinism is due to the functional problem in insulin receptor. This is due to diminished insulin binding or post receptor failure, or diminished insulin receptor number, arising from disorder of insulin regulation gene. There may be defective post receptor signal transduction, leading to disorder of serene phosphorylation.

Hyper-androgenism on the other hand, arises from the increase of active pituitary gonadotrophin (LH) receptors in thecal cells. Hyper-insulinaemia acts via Luteinizing Hormone (LH) receptors, leading to reduction in Sex Hormone Binding Globulin (SHBG) and increase in the free androgen level [4]. Obesity also contributes to hyper-androgenism, when DHEA-S is converted to testosterone more in fat cells, thereby imparting a synergistic effect in hyper-insulinaemia [5, 6].

In puberty, there is increase in growth hormone accelerated lipolysis, which in turn leads to the elevation of free fatty acids (FFA) [7], which replaces glucose from target oxidation. Increase in glucose level increases more insulin secretion, leading to physiological hyper-insulinaemia [4]. This in turn inhibits lypolysis and proteolysis, leading to a 'growth spurt' [8]. SHBG and IGFBP-1 (Insulin-like Growth Factor Binding Protein-1) are decreased; thereby the androgen level increases [4]. These changes are totally reversible after growth spurt is achieved. If hyper-insulinaemia persists, PCO develops due to genetic or environmental factors. The environmental factors like lifestyle derangement, economic and academic stress, and stress on sole child in one-child family also adds to the problem of PCOS.

The pubertal endocrinal changes associated with adolescent PCOS are divided into 4 axes –

1. Gonadotropic axis, which can generate abnormal GnRH pulse, temporary in puberty and persistent in adolescent PCO, leading to more LH, anovulation, and hyper-insulinaemia [9, 10]
2. Adreno-corticotropic axis, leads to abnormally high Adreno-Corticotropic Hormone (ACTH) secretion and elevation of prolactin (PRL) level. High secretion of estrogen leads to DHEA excess, resulting in abnormal cytochrome P450c 17ά activity [11]
3. Somato-trophic axis, where there is increase in the growth hormone, leading to hyper-insulinaemia and hyper-androgenism [12]
4. Intrinsic axis, where abnormal activities of ovarian and adrenal intrinsic cytochrome P450c 17 result in hyper-androgenism [13, 14]

Management of PCOS:

The primary modality of management may be lifestyle change, better known as lifestyle management, attempts at loss of weight through physical exercises, induction of positive attitude and re-arrangement of daily dietary habits. The medicinal help includes use of metformin judiciously, combination of estrogen-progesterone in the form of oral contraceptive pills (OCPs), anti-androgens or combinations of them, and the controlled use of estrogen, which manage PCO in adolescence. Low dose estrogen can be given during this period in less than 50 mcg daily dose, as low as possible. The parents of these girls are very much hesitant to use OCPs, due to common fear and social taboo. In these cases, low dose estrogen along with progesterone is used to maintain regular cycles. Regarding progesterone, Cyproterone Acetate (CPA), Drosperinone, Levonorgestrel (LNG) and Desogestrel, all are of similar importance. The selection depends on clinical presentation. In hirsutism and hypertrichosis, CPA is a better choice. Though it is hepatotoxic in pharmacological doses, a minimal dose of 2 mg of CPA and 30-35 mg dose of Ethinyl Estradiol (EE) per day acts at all levels as anti-androgens [15, 16] (vide Fig. 1). Drosperinone simulates mineralo-corticoids, but does not stimulate androgen production. Desogestrel does not stimulate any androgen secretion, while LNG acts as better haemostatic and cycle controller. It is always better to avoid laparoscopic ovarian drilling (LOD) in this age, as there are certain disadvantages of LOD in this age group.

Table 1 indicates the hormonal defects, single or combined in PCO, as obtained in our clinic and according to that, the choice of drugs gives better results.

Other anti-androgens presented in (Fig. 1) indicate that CPA is a rational and better anti-androgen amongst all.

Our Observation:

In the last 5 years from 2005-2010, total number of PCOS patients attending in Calcutta Fertility Mission, 21, Bondel Road, Kolkata, (West Bengal) India, were 3751, amongst which 452 were adolescent PCO patients. Their ages varied between 13-19 years. The hormones mentioned above were estimated in all of them, and different forms of hormonal defects were found out in (Table 1).

Table 1: Choice of Preparations in Adolescent PCO

Hormone Defects	CFM data (N=452)	Choice of Drugs
Only SI ↑	25%	Metformin
Only T ↑	9%	CPA + EE
T ↑ DHEA ↑	8%	Met + Dxm CPA + EE + Dxm
TSH ↑ SI ↑ T ↑	35%	L-thyxn + Met
TSH ↑ T ↑	18%	L-thyroxine
PRL ↑ DHEA ↑	5%	BCP/CBG + Dxm

SI - Serum Insulin, T - Testesterone, DHEA - Dehydroepiandrosterone, TSH - Thyroid Stimulating Hormone, PRL - Prolactin

Hypo-thyroid, hyper-insulinaemia and hyper-androgenism were found in maximum number of cases (35%), while hyper-prolactenaemia with hyper adrenalism was found in minimum number of cases (05%). The treatments continued accordingly, and it was also observed that the earlier treatment was introduced, the cure of clinical symptoms were long-lasting in later life, even after stopping the treatment in adulthood.

Conclusion:

Early detection of PCO in adolescence can prevent many recent or remote complications.

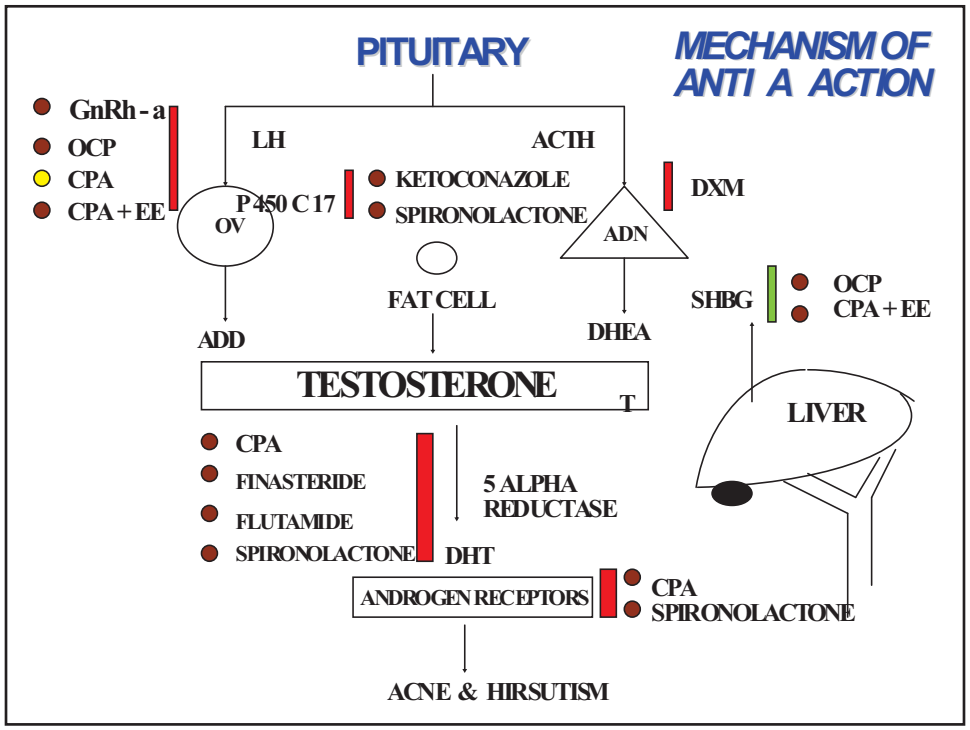

Fig. 1: Mechanism of Anti-Androgens Action

Initiation of treatment in early years leads to stabilization of the condition for a longer period, easily and successfully. Weight-reduction by diet restriction is the sheet anchor of over-weight adolescent PCO, which helps to lower the androgen and insulin levels. OCPs symptomatically reduce menstrual irregularities, and so also the androgen level. Anti-androgens like CPA though not available in pharmacological dose in this country and is also very hepatotoxic, a lower dose of 2 mg of CPA and 35 µgm of EE is effective in treating androgen excess and irregular menstruation. Alternatively, spironolactone may be used in 100-200 µgm daily dose, but its role in the treatment of adolescent PCOS is doubtful. Metformin alone or in combination with OCPs is very helpful in this age group of PCOS.

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