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Research Article

Evaluation of insulin resistance in adolescent girl with menstrual irregularities

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ABSTRACT

Background: Polycystic ovary syndrome is most commonly recognized endocrinopathy in reproductive age group. The symptoms of PCOS vary with age, race, weight, and medications, which lead to the challenges of accurate diagnosis particularly in adolescent age group. Adolescent with PCOS most commonly encountered by gynecologist, for their menstrual irregularities. During early puberty, menstrual irregularities can occur normally due to immature Hypothalamo-pituitary-ovarian axis. Early detection of PCOS is required to control high risk of insulin resistance followed by reproductive and metabolic consequences latter on in life. Also diabetes mellitus is asymptomatic at early stage of insulin resistance and impaired glucose tolerance. Few studies have been conducted in Indian population, for prevalence of insulin resistance and metabolic syndrome in adolescents with PCOS, with varying results and hence further study is required. The aim and objectives of the study was to evaluate the presence of insulin resistance in adolescents with menstrual disorders persisting 2 years after menarche.

Methods: A Cross sectional Study consisting of 102 adolescent girls done in Gynecology Outpatient Clinic of the Indira Gandhi Institute Of Medical Science Biochemical analysis was done on (day 3 to day 5) of menstruation for clinical/laboratory hyperandrogenism, and various cause of anovulation. HOMA-IR value was evaluated for insulin resistance by following formula: $\text{fasting serum insulin } (\mu\text{U/ml}) \times \text{fasting plasma glucose (m mol/l)} / 22.5$. The 2003 Rotterdam consensus workshop criteria were used for ultrasonographic feature of polycystic ovarian syndrome.

Results: Most common pattern of menstrual irregularities was Oligomenorrhea. 4 (7.84%) cases had insulin resistance ($\text{HOMA-IR} > 3.9$) and 25 (49.01%) cases had elevated HOMA-IR values ($\text{HOMA-IR} > 1$). PCOS was seen in 35.29% of cases and only 1.96% of control.

Conclusions: Adolescents with persistent menstrual irregularities even after two year of menarche, especially with oligomenorrhea and hypomenorrhoea, more frequently have the diagnosis of PCOS and also present with elevated HOMA-IR values.

Keywords: PCOS, Insulin resistance, HOMA-IR, Menstrual irregularities

INTRODUCTION

One of the most common gynaecologic and endocrine problems encountered by gynaecologists is Polycystic ovarian syndrome which importantly has both reproductive and metabolic consequences.¹ Menstrual

disorders and physical manifestations of excessive androgen production is the leading cause of consultation in adolescent group. Other than metabolic syndrome and primary infertility they are also at high risk for insulin resistance and impaired glucose tolerance. Therefore it is important to identify adolescent at risk, early because

diabetes mellitus is asymptomatic at early stage of insulin resistance and impaired glucose tolerance. Modification in life style can avert development of metabolic syndrome and diabetes mellitus in these adolescents.^{2,3} The menstruations pattern that follow menarche, especially during the first 2 years, are usually anovulatory, irregular, and occasionally abundant, due to the immaturity of the hypothalamus-pituitary-ovary axis in adolescents.⁴⁻⁶

After two year of menarche, the hypothalamus-pituitary-ovary axis usually acquires normal functioning. The persistence of anovulatory cycles for more than 24 months after menarche, especially in association with other characteristics of hormonal disorders, suggest ovulatory dysfunction of pathologic origin.^{7,8}

The 2003 Rotterdam consensus workshop⁹ concluded that PCOS is a syndrome of ovarian dysfunction, and that for its diagnosis two of three criteria must be present. The three criteria established at this consensus are: (1) chronic anovulation characterized by persistent menstrual irregularity for more than six months; (2) clinical and/or laboratory hyperandrogenism; and (3) ultrasonographic appearance of the polycystic ovary.

The ultrasonographic feature of polycystic ovary are based on (1) ovarian volume (larger than 10 cubic cm without functional cysts), (2) number of micro cysts sized 2 to 9 millimetres in mean diameter on gonadal periphery, and (3) stroma echogenicity.¹⁰

Insulin resistance, Which is related to a post-insulin receptor defect that course with compensatory hyperinsulinemia in addition to other factors such as reduction of hepatic insulin clearance and increased pancreatic sensitivity leading to an abnormal biological response, with increased circulating insulin concentration, is the central pathogenesis of anovulation.^{3,11-16} This hyperinsulinemia is responsible for the development of hyperandrogenism that induces anovulation.^{5,6,17,18} To combat the economic burden of PCOS screening, diagnosis, and intervention is required to prevented or ameliorated the serious complication of diabetes mellitus and is therefore justifiable.^{19,20}

As few Studies are conducted in Indian population, for prevalence of insulin resistance and metabolic syndrome in adolescents with PCOS, with varying results and hence further study is necessary.²¹⁻²³

Present study is conducted to evaluate the presence of insulin resistance in adolescents with menstrual disorders at least 2 years after menarche and to determine the presence of PCOS.

METHODS

Study design

It was a Cross sectional Study consisting of 102 adolescent girls, aged 12 to 19 years, selected from patients attending the Gynecology Outpatient Clinic of the Indira Gandhi Institute of Medical Science. Informed consent was taken.

The patients were divided into two groups: group I (study group) had 51 adolescents presenting with menstrual irregularities such as oligomenorrhea, amenorrhea, or polymenorrhoea, and Group II included 51 adolescents with normal menstrual cycles.

Adolescents aged 12 to 19 years at least 2 years post – menarche with Menstrual disorders such as amenorrhea, oligomenorrhea (≤ 6 menses per year), polymenorrhoea were included in study, whereas > 19 years of age ,taking medications [OCP > 3 years , steroids etc.] that may interfere with hypothalamus-pituitary-ovary axis and with any medical or surgical disease were excluded from study.

Methodology thorough clinical examination was done after detail history of patients. Signs of hyperandrogenism were noted. Clinical hyperandrogenism was considered to be present when the Ferriman-Gallway index was ≥ 8 , with/without presence of hair loss, acne, or oily skin.²⁴

On day 3 of menstrual cycle all adolescents went through following biochemical analysis: Serum levels of testosterone, 17-hydroxyprogesterone, and DHEA-S (to establish laboratory hyperandrogenism, characterized by testosterone levels ≥ 120 ng/dl, 17-hydroxyprogesterone ≥ 140 ng/dl and DHEA-S (dehydroepiandrostenedione sulphate) levels ≥ 250 μ g/dl).

To diagnose disorders of glucose metabolism, blood glucose and insulin levels were obtained after an 8- to 12-hour fast. An oral glucose tolerance test was done with 75 g dextrose and glucose and insulin were determined at 0, and 2 hours. To evaluate insulin resistance, HOMA-IR value was obtained by: fasting serum insulin (μ U/ml) \times fasting plasma glucose (mmol/l)/22.5. An ideal normal-weight individual aged < 35 years has a HOMA-IR of 1.0 mol \times μ U/L2 whereas HOMA value > 3.90 mol \times μ U/L2 was considered as insulin resistance.²⁵⁻²⁷

For exclusion of other cause of anovulation Hb, TC, DC, ESR, URINE (Routine and Microscopy), Prolactin (PRL), TSH, T3, T4, FSH, LH was obtained.

By ELISA, Luteinizing hormone, follicle stimulating hormone (FSH), PRL, TSH, testosterone, DHEA-S, 17 hydroxyprogesterone (17-OHP), insulin were obtained and plasma glucose was obtained by the exokinase method.

All adolescents went through transabdominal pelvic ultrasound in follicular phase (day 3 to 5) for the evaluation of the morphological aspect of the ovaries. The ultrasonographic polycystic ovary were characterised by (1) ovarian volume (larger than 10 cubic cm without functional cysts), (2) number of micro cysts sized 2 to 9 millimetres in mean diameter on gonadal periphery, and (3) stroma echogenicity.

Adolescents were considered to have PCOS when two of the following three criteria were found- (1) chronic anovulation characterized by persistent menstrual irregularity for over six months; (2) clinical and/or laboratory hyperandrogenism; and (3) ultrasonographic appearance of the polycystic ovary.⁹

The same parameters were determined in group II (control group) and prevalence of PCOS, obesity, and insulin resistance were compared between two groups.

RESULTS

Table 1: Age distribution.

Age (years)	Cases	Controls	P value
12-15	2(3.9%)	7(13.7%)	0.28
16-19	49(96.07%)	44(88.27%)	
Total	51(100%)	51(100%)	

It was a cross-sectional study and results were analysed by applying following statistical methods- Student t test/Mann-Whitney test wherever applicable for data analysis, p value <0.05 was considered as significant.

For cases mean age were 17.84 years and for controls were 17.24 years. P value determined by t-test was not significant.

Table 2: Pattern of menstrual irregularities.

Pattern of menstrual irregularities	No. Of cases
Oligomenorrhea	40(78.43%)
Hypomenorrhoea	6(11.76%)
Amenorrhoea	1(1.96%)
Polymenorrhoea	4(7.84%)
Total	51(100%)

Oligomenorrhea, followed by hypo/polymenorrhoea was most common pattern of menstrual irregularities.

Clinical signs of hyperandrogenism: 14 (27.45%) of cases versus none among controls had hirsutism, Acne was present in 9 (17.64%) cases and 4 (7.84%) controls, whereas 3 (5.88%) cases versus none of controls had temporal pattern of hair fall.

P value obtained by Mann-Whitney test was 0.001, which was highly significant.

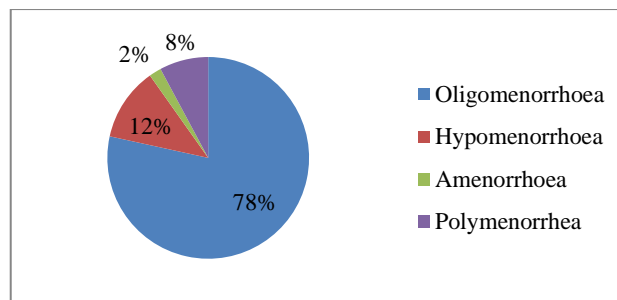


Figure 1: Pattern of menstrual irregularities.

By Mann-Whitney test p value obtained for both parameters, was 0.001, which was highly significant. None of the cases or controls had increased Prolactin, TSH, or progesterone levels.

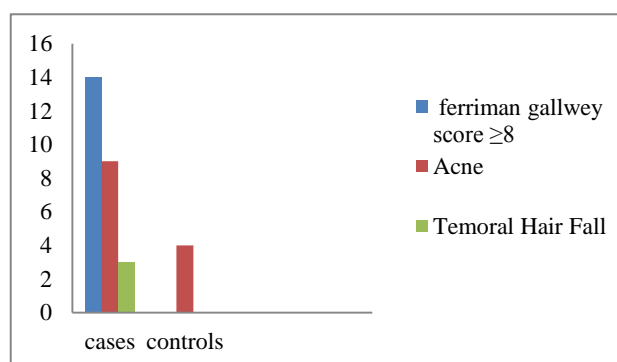


Figure 2: Clinical signs of androgenism.

Table 3: Hyperandrogenism on laboratory evaluation.

Serum Testosterone (≥120 ng/dl)	Cases	Controls	P value
	7(13.72%)	3(5.88%)	0.001

Serum DHEAS ≥250 µg/dl	Cases	Controls	P value
	4(7.84%)	1(1.96%)	0.001

Table 4: HOMA-IR.

HOMA-IR	Cases	Control	P value
<1	22(43.13%)	47(92.15%)	0.001(highly significant)
>1	25(49.01%)	4(7.84%)	
>3.9	4(7.84%)	0	

In 29 (56.82%) cases HOMA-IR was elevated but in controls only 4 (7.84%). Insulin resistance was present in 4 (7.84%) cases. P value (0.001) was calculated by Mann-Whitney test, which was highly significant. Insulin resistance (HOMA-IR>3.9) was present in 4 (7.84%) cases, elevated HOMA-IR values (HOMA-IR >1) in 25 (49.01% cases), whereas only 4 (7.84%) controls had elevated HOMA-IR value.

Of 29 cases with elevated HOMA-IR value, 20 (69%) had BMI ≥ 25 kg/m². None of the cases or controls had abnormal fasting or postprandial glucose levels (but postprandial blood sugar value was toward higher side, which show a significant difference with control group).

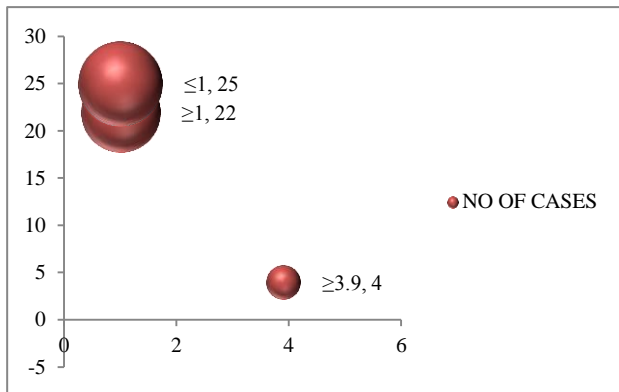


Figure 3: HOMA-IR values in cases.

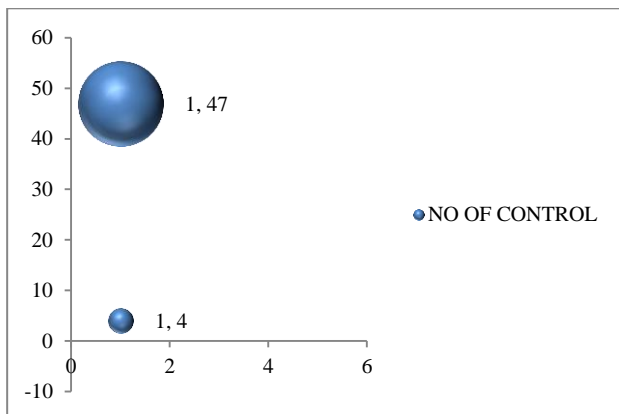


Figure 4: HOMA-IR values in cases.

Table 5: PCOS (Rotterdam criteria).

PCOS	cases	Controls
	18(35.29%)	01(1.96%)

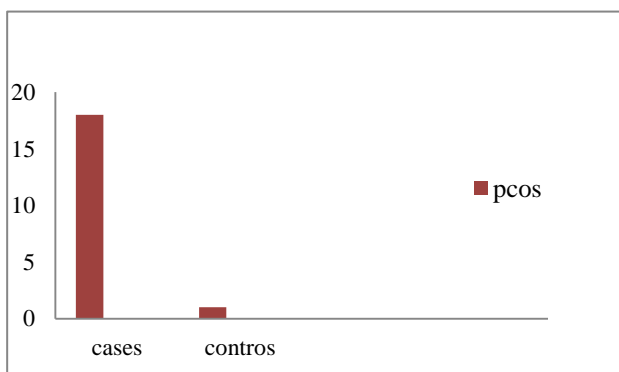


Figure 5: PCOS.

18 (35.29%) cases but only 01 (1.96%) controls met the Rotterdam criteria of PCOS. Of the 18 cases with PCOS, 14 had elevated HOMA-IR (10 with HOMA-IR > 1 ; 4 with insulin resistance i.e. HOMA-IR > 3.9). In control with PCOS, HOMA-IR was > 1 but < 3.9 .

Table 6: Pattern of menstrual irregularities in cases with PCOS.

Pattern of menstrual irregularities	No. of Cases with PCOS
Oligomenorrhea	15
Hypomenorrhoea	2
Amenorrhoea	0
Polymenorrhoea	1
Total	18

So oligomenorrhea, hypomenorrhoea and polymenorrhoea are the startling pattern of menstrual irregularities for early detection of polycystic ovarian syndrome in adolescent age group.

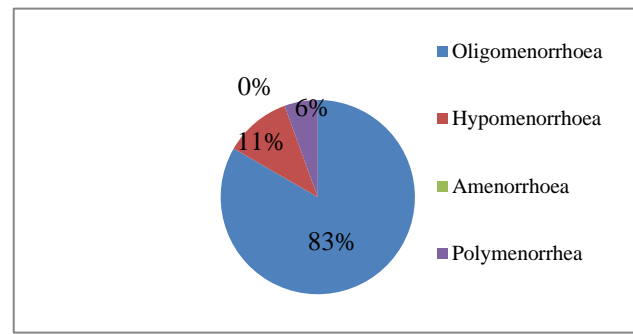


Figure 6: Pattern of menstrual irregularities in case of PCOS.

Table 7: Pattern of menstrual irregularities in cases with HOMA-IR.

Pattern of menstrual irregularities	No. of Cases with HOMA-IR >1
Oligomenorrhea	20
Hypomenorrhoea	5
Amenorrhoea	0
Polymenorrhoea	4
Total	29

Out of 29 patient with HOMA-IR value >1 , 20 cases where presented with oligomenorrhea and 5 with hypomenorrhoea followed by 4 with polymenorrhoea.

DISCUSSION

There are major difficulties in the early diagnosis of PCOS during adolescence, because of confusion with clinical sign and symptoms of PCOS and the clinical characteristics and endocrine changes that occur during the first years after menarche, (which is physiologic

alterations during pubertal period).^{5,28,29} In the present study, p value was not significant for mean age of presentation. Oligomenorrhea (78.43%) was the most common pattern of menstrual irregularity, followed by hypomenorrhea (11.76%) for clinical presentation, as well as pattern of menstrual irregularities in association with, PCOS elevated HOMA-IR value and insulin resistance.

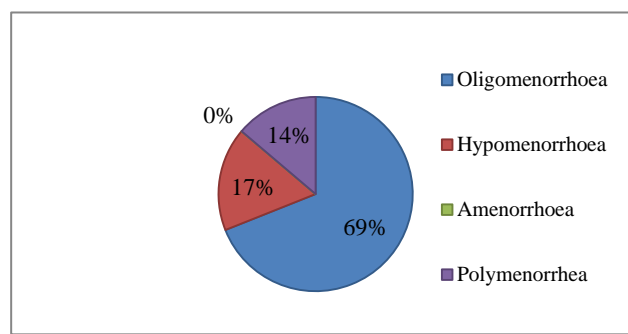


Figure 7: Pattern of menstrual irregularities in cases with HOMA-IR.

With hirsutism (Ferriman-Gallway score more than 8), 14 (27.45%) of adolescents presented with menstrual irregularity, while none of the adolescents with regular menstrual cycles presented with hirsutism (p value <0.05).

On the other hand, Avvad et al stated that the presence of hirsutism can be simply the expression of increased skin sensitivity to normal levels of circulating androgens and does not necessarily indicate an abnormal ovulatory mechanism in this patients.⁷

Various literature shows that the levels of free testosterone, LH, and the LH/FSH ratio in adolescents with menstrual irregularity with no clinical signs of hyperandrogenism are similar to those of patients with PCOS and higher than those of adolescents with regular menstrual cycles.^{3,7,18,28}

In present study, we found significantly higher LH levels (p value<0.5), but not FSH levels (p value 0.4) in adolescent presenting with menstrual irregularities i.e.13 of 18 adolescents who met the Rotterdam criteria of PCOS had raised LH levels. The mean testosterone and DHEA-S levels in adolescents with menstrual irregularity were significantly higher than the control group.

On analysis of ultrasonologic finding we observed that ovarian volume was larger in cases than in controls supported by Rotterdam consensus for PCOS syndrome. 18 (35.29%) cases versus 01 (1.96%) controls met the Rotterdam criteria of PCOS.⁹ Perhaps the evaluation was precocious, clinical manifestations of hyperandrogenism were not yet present in all cases who met Rotterdam criteria of PCOS, but these findings agree with other authors who point to menstrual irregularity as the most

precocious marker of PCOS.^{3,5,6,8} Normal levels of 17OH progesterone, prolactin, and TSH described in these adolescents exclude the diagnosis of non-classic congenital adrenal hyperplasia, hyperprolactinemia and hypo or hyperthyroidism as a cause of menstrual disorders and clinical manifestations. A relation between PCOS and increased serum insulin levels have been described and supported by many investigators (Dunaif et al, Holte et al).^{30,31} It seems that insulin-like growth factor (IGF-like) has the capacity to stimulate the follicular theca cell layer to produce ovarian androgens. The similarity between molecular structure of insulin and IGF-like permits a cross match in the theca's receptors, so high serum levels of insulin, which happen in cases of peripheral insulin resistance (receptor defect), leads to increased secretion of androgens by the ovary, more than its capacity to convert androgen in estrogen.

The excess of androgen results from an inappropriate extra glandular contribution of estrogen (estrone), derived through the peripheral conversion. The elevated level of androgen inhibits the pituitary secretion of dopamine and so it allows a higher secretion of gonadotropins, especially LH, which also stimulates the theca cell layer to produce androgens.

During puberty, insulin sensitivity is usually decreased, causing increased secretion of androgen hormone.¹⁰ Some studies have assessed insulin resistance in adolescents with PCOS.^{19,32-34} The gold standard method for the diagnosis of insulin resistance is the hyperinsulinemic euglycemic clamp, a venous glucose tolerance test frequently used in experimental and scientific investigations but still very difficult to perform in clinical practice.³⁵ Although there still is no consensus about the best method for the detection of this disorder, the HOMA-IR has been considered to be a good diagnostic parameter.^{36,37} In the present study we calculated the insulin resistance with HOMA-IR method, which showed more elevated values in patients with menstrual irregularities than in controls (P value <0.01), which demonstrate the lower insulin sensitivity in these patients.

Avvad et al did not obtain the same result, when they compared adolescents with menstrual irregularities and hyperandrogenism to normal adolescents, even with similar insulin levels.⁷ In our study we calculated the fasting and postprandial glucose levels, none of the adolescents, either cases or controls, had abnormal values, probably because the elevation in the glucose levels begins only when (even with high serum insulin levels) the receptor resistance is such that the glucose levels cannot be controlled; in this stage the patient may present glucose intolerance, a step that leads to type II diabetes later on.

CONCLUSIONS

Treating the hypertension does not alter the progression of disease but early treatment decreases not only the

frequency of hypertensive crisis, but also the rate of neonatal complications. Antihypertensive medications are mainly used to prevent or treat severe hypertension, to prolong pregnancy for as long as safely possible thereby maximizing the gestational age of the infant, and to minimize fetal exposure to medications that may have adverse effects.

This study confirms the previous findings that labetalol is an effective and safe drug for use in the control of blood pressure in pregnancy-induced hypertension. The low incidence of maternal and foetal side-effects together with the excellent perinatal outcome in a condition usually accompanied by a high maternal and foetal mortality and morbidity confirms its suitability for use during pregnancy. Nifedipine is equally efficacious and better tolerated compared to methyldopa in the treatment of new onset hypertension during pregnancy. However, the effect on fetal and maternal outcomes must be considered before selecting any drug in the treatment of hypertensive disorders of pregnancy.

Awareness regarding PIH and availability of easily accessible and affordable health care services to rural population and poor people is important which shall be helpful in reducing the PIH related morbidity and mortality.

CONCLUSION

With the present study we conclude that there was a significant association between pattern of menstrual irregularity, elevated HOMA-IR value, and PCOS. 15 out of 18 cases with PCOS and 20 out of 29 cases with elevated HOMA-IR presented with oligomenorrhea, the most common pattern of menstrual irregularity in this series.

Based on these findings in present study, we concluded that adolescents with persistent menstrual irregularities, (especially oligomenorrhea and hypomenorrhoea), 2 years after menarche have the diagnosis of PCOS and also present with more elevated HOMA-IR values than controls, which indicate a great probability of the presence of insulin resistance and provide a unique opportunity to detect patients early in their lives and suggest measures that would prevent development of type II diabetes mellitus and reproductive abnormalities in later lives.

Since our study was conducted on small group of patients, hence, specific controlled studies on the population of patients with PCOS are necessary.

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