

Menstrual Phenotypes in Relation to Insulin Resistance in Infertile Women with Polycystic Ovary Syndrome

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Abstract:

Objective: To explore the menstrual phenotypes associated with endocrine, metabolic characteristics of infertile women with polycystic ovary syndrome.

Materials and methods : The cross sectional study was carried out among 125 infertile women with polycystic ovary syndrome attending Infertility wing of the Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2017 to December 2017. The women were evaluated by clinical history, examination, transvaginal sonogram and for endocrine and metabolic parameters. The women were divided into 5 groups according to their menstrual phenotypes: i) cycle length 21-35 days ii) oligomenorrhoea or cycle length > 35 days but less than 6 months iii) secondary amenorrhoea or cycle length ≥ 6 months iv) polymenorrhoea or cycle length <21 days v) oligomenorrhoea alternating with polymenorrhoea. One way ANOVA was used for analyzing the variance between groups. Categorical variables were analyzed for association by Fishers Exact Test and Chi Square tests where appropriate.

Results: A total of 125 women were recruited for the study. The women were divided into 5 groups according to their menstrual phenotype: i) cycle length 21-35 days (n=5) ii) oligomenorrhoea or cycle length > 35 days but less than 6 months (n=70) iii) secondary amenorrhoea or cycle length ≥ 6 months (n=35) iv) polymenorrhoea or cycle length <21 days (n=2) v) oligomenorrhoea alternating with polymenorrhoea (n=13). Accordingly the women with oligomenorrhoea with or without polymenorrhoea was most frequent (65%) followed by women with secondary amenorrhoea (27%), regular cycle (0.04%) and isolated polymenorrhoea (0.01%). One way ANOVA revealed significant difference between groups in fasting insulin and serum testosterone level. There is significant association of oligomenorrhoea (with or without polymenorrhoea) with insulin resistance (HOMA-IR ≥ 2). There is significant association of secondary amenorrhoea with hyperinsulinaemia (Fasting insulin ≥ 10 mIU/L) and insulin resistance (HOMA-IR ≥ 2).

Conclusions: Menstrual history of infertile women with polycystic ovary syndrome can be a clinical marker of insulin resistance and related metabolic risk.

Key words: Polycystic ovary syndrome, Oligomenorrhoea, Amenorrhoea, Insulin resistance

Introduction:

Infertility or sub-fertility means failure to conceive within one year of conjugal life. In a country where early marriage and pregnancy is the prevalent social norm, infertility is devastating problem. Polycystic ovary syndrome (PCOS) is a major cause of infertility in young women. PCOS is a chronic endocrine disorder that begins shortly after adolescence. Initially it presents with infrequent, sometimes prolonged

menstruation. Gradually androgenic features like excess facial and body hair and acne intervene. Androgenic features are sometimes not that marked and diagnosis is suspected by sonographic findings of enlarged polycystic ovary.

PCOS is a complex disorder of androgen excess and chronic anovulation involving multiple genetic and environmental factors ¹. The pathogenesis of PCOS

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involves insulin resistance and resultant hyperinsulinemia potentiates the secretion of luteinizing hormone (LH) from hypothalamo-pituitary system. LH and insulin synergistically stimulates ovarian androgen production. High intra-ovarian androgen arrests follicular maturation and ovulation². Anovulation leads to persistent estrogen stimulation of endometrium and absence of the stabilizing effect of progesterone leads to breakthrough bleeding at different intervals. So anovulation in women with polycystic ovary syndrome (PCOS) is expressed as menstrual abnormality³. Around 15% of women with PCOS have regular menstrual cycle but without regular ovulation. Others have oligomenorrhoea with cycle length >35 days. The cycle length may extend up to more than 6 months which in other words is secondary amenorrhoea. Some women have only withdrawal bleeding where menstruation is induced only by short courses of progesterone. Some women have polymenorrhoea or cycle length less than 21 days. Sometimes women have oligomenorrhoea alternating with polymenorrhoea or prolonged menstruation⁴. This abnormal uterine bleeding categorized as anovulatory bleeding is a bothersome symptom for women with PCOS.

Since anovulation in women with PCOS has been linked to insulin resistance, we would like to see if menstrual cycle length reflects the severity of insulin resistance. There may be other associated changes in the hormone profile of the women since PCOS is a chronic endocrine disorder. The objective of this study is to see if there is any association of menstrual phenotypes with endocrine and metabolic profile in terms of insulin resistance in infertile women with PCOS.

Method:

This was a cross sectional study of 125 infertile women with polycystic ovary syndrome who attended the Infertility wing of the Department of Obstetrics and Gynaecology at Bangabandhu Sheikh Mujib Medical University, Dhaka during the period of January 2017 to December 2017. The women attended sequentially, consented for study participation and were recruited at first visit. They were not exposed to metformin or the lifestyle modification during prior three months. They were not exposed to any oral contraceptive pills for cycle regulation, hirsutism or as contraceptive method

The women were evaluated by clinical history, examination, TVS (transvaginal sonogram) and for endocrine and metabolic parameters. Eligibility criteria were infertile women with age range 15-40 years and any two of the following: i) infrequent

menstruation (cycle length >35 days), ii) hirsutism with modified Ferriman Galway score ≥ 8 , iii) at least one enlarged (>10cm³) polycystic ovary at TVS⁵. The selected women were divided into 5 groups according to their menstrual phenotype: i) cycle length 21-35 days ii) oligomenorrhoea or cycle length > 35 days but less than 6 months iii) secondary amenorrhoea or cycle length ≥ 6 months iv) polymenorrhoea or cycle length <21 days v) oligomenorrhoea alternating with polymenorrhoea.

Anthropometric measurements:

BMI: Weight was measured on a beam scale to within 0.1 kg in light clothing without shoes. Subjects stood straight with both feet in firm contact with the surface, looking ahead with hands not touching any surface. Heights were measured to 0.1 cm using a wall mounted stadiometer. BMI was calculated as weight in kg divided by the square of height in meters.

WC: Waist circumference was measured to the nearest 0.1 cm with a non stretchable measuring tape. The subject stood straight with a single layer of clothes around abdomen. The tape was placed, at the end of exhalation, horizontally between the last floating rib or lower costal margin and the iliac crest. Hip circumference was measured to the nearest 0.1 cm at the level of pubic symphysis and the point of greatest posterior extension of the buttocks. The waist circumference was divided by hip circumference to give waist hip ratio.

Biochemical Assay: All the women had hormone analysis, oral glucose tolerance test and fasting lipid profile. The tests were done in the Department of Biochemistry and Molecular Biology of Bangabandhu Sheikh Mujib Medical University. Fasting blood samples were drawn in follicular phase cycle on days 2-5. This was to avoid any possible effects of sex steroids on insulin action. Venous blood samples were drawn after an overnight fast of at least 8 hours. Fasting blood glucose was measured by hexokinase method (CI4100 ARCHITECT USA). All hormones were measured by Chemiluminiscent Microparticle Immunoassay (CI 4100 ARCHITECT USA).

Cut off values: Cut off value for waist circumference for Asian women for defining central obesity is ≥ 80 cm (International Diabetes Federation)⁵. Hyperandrogenemia was defined when serum total testosterone was > 60ng/ml. High LH:FSH ratio was >1. The cut off value of hyperinsulinemia was ≥ 10 mIU/L and the cut of value of insulin resistance was HOMA IR ≥ 2 . Fasting insulin was 9.25 μ IU/mL at 75th percentile for Pakistani population⁶. HOMA-IR was 1.93 at the 75th percentile for Indian population

and 1.82 at the 75th percentile of Pakistani population⁶. For the sake of simplicity we rounded up the cutoff value HOMA-IR at 2 and the cut-off value of fasting insulin at 10mIU/L.

Statistical analysis: Statistical analysis was done by SPSS (Statistical Package for Social Science) version 22. One way ANOVA was used for analyzing the variance between groups. Categorical variables were analyzed for association by Fishers Exact Test and Chi Square tests where appropriate. Statistical significance (two tailed) was defined as $p \leq 0.05$.

Ethical issues: Consent were taken from the participants regarding participation in the study. Permission from the head of the infertility wing was obtained before starting actual procedure. Data collection was accomplished by maintaining adequate privacy and confidentiality and without any physical harm abiding by Helsinki declaration.

Results:

A total of 125 women were recruited for the study. The women were divided into 5 groups according to their menstrual phenotype: i) cycle length 21-35 days (n=5) ii) oligomenorrhoea or cycle length > 35 days but less than 6 months (n=70) iii) secondary amenorrhoea or cycle length ≥ 6 months (n=35) iv) polymenorrhoea or cycle length <21 days (n=2) v) oligomenorrhoea alternating with polymenorrhoea (n=13). Accordingly the women with oligomenorrhoea with or without polymenorrhoea was most frequent (65%) followed by women with secondary amenorrhoea (27%), regular cycle (0.04%) and isolated polymenorrhoea (0.01%). There were some missing values as all data were not available for all study participants. The missing values were excluded from analysis.

Table I summarizes the means of different anthropometric, endocrine and metabolic parameters of different menstrual groups with confidence

Table-I
anthropometric and endocrine parameters in infertile PCOS women of different menstrual phenotypes.

Parameters	Group i Regular cycle (n=5)		Group ii Oligomenorrhoea (n=70)		Group iii Secondary amenorrhoea (n=35)		Group iv Polymenorrhoea (n=2)		Group v Oligomenorrhoea alternating with polymenorrhoea (n=13)	
	Mean±SD	95% CI for mean	Mean±SD	95% CI for mean	Mean±SD	95% CI for mean	Mean±SD	95% CI for mean	Mean±SD	95% CI for mean
Age	27.6±4.0	22.632	25.5±3.7	24.726.4	25.7±4.0	24.3 27.1	23±0	23-23	25±3.9	22.3 27.6
BMI	28.6±4.5	23.0 34.2	26.4±3.1	25.727.2	26.7±3.2	25.6 27.8	27.1±3.6	-5.5 59.7	25.6±2.6	24.027
WC	92.5±15.3	68.0 116.9	90.8±9.1	88.493.1	92.6±9.6	89.2 95.9	88.5±9.19	5.9171	86.8±8.5	81.4 92.2
WHR	0.89±0.07	0.771	0.92±0.12	0.880.93	0.91±0.06	0.88 0.93	0.89±0.02	0.70 1.08	0.87±0.05	0.84 0.90
Serum FSH	5.31±0.83	4.25 6.34	5.15±1.82	4.725.59	5.10±1.86	4.45 5.74	4.22±0.12	3.27 5.17	5.44±1.52	4.52 6.36
Serum LH	8.49±4.17	3.31 13.68	8.22±5.38	6.949.51	7.88±5.83	5.88 9.89	9.65±5.72	-41.8 61.11	8.55±6.08	4.90 12.19
LH: FSH ratio	1.5±0.6	0.72.3	1.7±1.1	1.41.9	1.7±1.4	1.22.2	2.2±1.3	-9.4 13.9	1.6±1	0.1-2.2
Serum total testosterone	55.42±20.96	3.33 107.51	45.37±32.1	35.8354.91	63.65±34.61	48.69 78.62	124 (1 missing value)		69.07±47.37	32.66 105
Serum TSH	3.24±1.15	1.81 4.67	2.83±1.45	2.483.18	2.28±1.49	1.76 2.82	2.05±1.85	14.59 18.69	1.87±1.28	1.07 2.70
Serum prolactin	9.76±7.86	-0.01 19.53	14.48±11.53	11.6717.29	12.18±6.24	9.92 14.43	12.50±3.82	21.80 46.80	12.06±4.93	8.93 15.20
Serum fasting insulin	19.10±12.06	4.11 34.08	15.15±10.44	15.67±12.31	11.45±20.19	12.60 17.70	56.25±16.61	-93.04 205.54	17.23±14.32	3.13 26.33
HOMAIR	1.1±0.9	-1.2.4	2.2±2.1	1.7-2.7	1.5±1.2	1.1-1.9	0.8±1.08	-8.8 10.5	1.3±0.9	0.8-1.8

Table-II
Association of menstrual phenotypes with insulin resistance and hyperandrogenemia (two tailed significance p values)

Parameters	Regular cycle (21-35 days)	Oligomenorrhoea >35 days , < 6 months	Secondary amenorrhoea >6 months	Polymenorrhoea <21 days	Oligomenorrhoea alternating with polymenorrhoea
Hyperinsulinaemia (Fasting insulin >10mIU/L)	0.136	0.141	<0.05*	0.111	0.122
Insulin resistance (HOMA-IR>2)	0.230	<0.05*	<0.05*	0.202	0.144
Hyperandrogenemia (total testosterone >60ng/ml)	0.204	0.057	0.611	0.052	0.878

· Statistically significant associations of hyperinsulinaemia and insulin resistance with secondary amenorrhoea and oligomenorrhoea

intervals for means calculated during test of ANOVA. A confidence interval for mean gives us a range of plausible values for the population mean. One way ANOVA revealed significant difference between groups in fasting insulin and serum testosterone. There was no significant difference in anthropometric or other hormonal parameters between the groups. To see association of hyperinsulinaemia (fasting insulin >10IU/L), insulin resistance (HOMA-IR >2) and hyperandrogenemia (total serum testosterone >60ng/ml) with different menstrual phenotypes, 2x2 contingency table were built for chi square and fisher's exact test (Table II). The analysis displays significant association of oligomenorrhoea (with or without polymenorrhoea) with insulin resistance. There was a significant association of secondary amenorrhoea with hyperinsulinaemia and insulin resistance also.

Discussion:

The objective of the study was to find out any significant association of anthropometric, endocrine parameters and insulin resistance with menstrual phenotypes. Significant association of oligomenorrhoea and amenorrhoea with insulin resistance was found.

Regarding prevalence of cycle abnormalities, the women with oligomenorrhoea with or without polymenorrhoea were most frequent (65%) followed by women with secondary amenorrhoea (27%), regular cycle (0.04%) and isolated polymenorrhoea (0.01%). Approximately 15- 40% of women with PCOS have regular cycle but diagnosed to have PCOS on the basis of hirsutism and polycystic ovary^{3,4}. In another study⁷ about 20% of the PCOS women had menstrual cycles less than 35 days (ie with

polymenorrhoea or clinically apparent eumenorrhoea). Polymenorrhoea is very uncommon, observed in less than 2% of untreated women with PCOS⁸. Our study shows much less prevalence of women with cycle less than 35 days probably because women in this group do not have persistent anovulation and so are relatively fertile.

A cross sectional study⁷ of four hundred and ninety four women diagnosed with PCOS by the Rotterdam criteria and eumenorrhoeic non hirsute control women evaluated the relationship between the severity of menstrual dysfunction and the degree of insulin resistance measured by HOMA-IR. After adjusting for BMI, age and race, all PCOS women having menstrual cycles longer than 35 days had significantly higher mean HOMA-IR levels than controls and those with cycles longer than 3 months had the highest HOMA-IR levels. There was a large prospective study of 1285 women with PCOS to assess the relationship between the type of menstrual cycle irregularities and insulin resistance⁹. Women with secondary amenorrhoea and oligomenorrhoea had more insulin resistant than women with regular cycles. Oligomenorrhoea displayed less excessive risk of insulin resistance than amenorrhoea. Strotzski et al¹⁰ showed that PCOS women who are normocyclic had better metabolic parameters (BMI, fasting insulin and insulin resistance) than those with oligomenorrhoea or amenorrhoea. Hormonal parameters like serum levels of LH and testosterone were significantly different in women with different menstrual patterns. There are population based studies showing higher prevalence of diabetes mellitus in women with irregular cycles¹¹. So our

findings are supported by a number of large studies.

Our study suggests that secondary amenorrhoea is significantly associated with hyperinsulinaemia and insulin resistance in infertile women with PCOS. Excess insulin directly induces excess ovarian androgen and ovarian follicular arrest. Persistent anovulation in women with amenorrhoea can be explained by excessive hyperinsulinaemia and insulin resistance in these women. Secondary amenorrhoea in these women also heralds increased metabolic risk related to insulin resistance. When insulin sensitizers are given, reduction in insulin resistance may be clinically apparent in reducing cycle length from amenorrhoea to oligomenorrhoea.

Oligomenorrhoea is significantly associated with hyperinsulinaemia, the one basic change in the pathophysiology of PCOS. This explains oligomenorrhoea as the frequent menstrual abnormality in PCOS women. The hyperinsulinaemia reflects excess production of androgen by ovary and ovarian hyper-androgenism inducing ovarian follicular arrest. Further clinical trials on the effect of insulin sensitizers on menstrual cycles of PCOS women may be undertaken.

Our study comprised a selected group of women with PCOS who sought medical attention for infertility. They may represent a more severe phenotype of menstrual abnormalities than unselected population of PCOS women¹². The sample size is moderate leading to inadequate power of the study.

Conclusion:

Oligomenorrhoea is associated with insulin resistance in infertile women with PCOS. Clinical assessment of menstrual irregularities such as oligomenorrhoea and amenorrhoea can predict the presence and severity of insulin resistance in women with PCOS. Menstrual history can be a clinical marker to identify the infertile women with PCOS at greater risk of metabolic derangement.

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