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Clinical And Biochemical Features In PCOS Among Women With Infertility

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ABSTRACT

Objectives: To asses clinical features and metabolic disorders in PCOS; to find out relationship of PCOS with Infertility. **Background:** Polycystic ovarian syndrome (PCOS) is a common endocrine condition affecting women of reproductive age. It is characterized by chronic anovulation, hyperandrogenism and polycystic ovaries. Worldwide prevalence of PCOS ranges from 4% to 21%. **Aims and objectives:** The aim of this study was to determine prevalence of polycystic ovaries (PCO) and associated clinical and biochemical features among women with infertility attending gynaecological outpatient department (GOPD) at one government hospital and one private chamber in upazilla level, Bangladesh. **Methods:** Women with infertility attending from july 2021 to June 2022 were recruited to the study. Information on socio-demographic, obstetric, menstrual and other characteristics was collected. Clinical examination of acne, acanthosis nigricans and hirsutism, vaginal ultrasonography for PCO and biochemical analysis of luteinizing hormone (LH), follicle stimulating hormone (FSH), AMH, serum prolactin and testosterone were performed. Metabolic disorders were identified by measuring blood pressure, cholesterol level and Body Mass Index (BMI). **Results:** In this study it was found that 59% patients were obese among PCOS patients 90% were in ovulatory dysfunction. 66% PCOS patitents had hirsutism, 59% patients had acne, and 46% had impaired glucose tolerance. This study revealed that 41% PCOS patients had high TG level, 63% had LH: FSH more than 2 that was significant.

Keywords: *Clinical and biochemical features, PCOS, women, Infertility.*

INTRODUCTION

Diagnosing PCOS is a challenge with changing criteria and different definitions. While the National Institutes of Health (NIH) criteria from 1990 are strict and include only anovulation and hyperandrogenism (HA; Dunaif and Thomas, 2001), the Rotterdam consensus criteria of 2003 are broader and include polycystic ovarian morphology (PCOM) as a criterion (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). More recently, the AES have proposed that HA should be mandatory for the diagnosis (Azziz et al., 2006). The first formal attempt to classify PCOS was carried out at a National Institute of Child Health and Human Development of the US National Institutes of Health (NIH) conference, April 1990. A tabulation of participant impressions indicated that clinical or biochemical hyperandrogenism (HA) and chronic oligo-anovulation (OA), after the exclusion of related disorders were considered key diagnostic PCOS features. The second definition was based on the consensus opinion of 27 PCOS experts, who met in Rotterdam, the Netherlands, May 2003 (Rotterdam ESHRE/ASRM, 2004). The conference was partially sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). As a result of this meeting, ultrasound characteristics for polycystic ovarian morphology (PCOM) were added to the NIH 1990

definition, making it more complex. The ESHRE/ASRM 2003 PCOS criteria required the presence of two of the following three findings:
1) Signs of clinical or biochemical HA;
2) Chronic ovulatory dysfunction (OD); and
3) PCOM, after exclusion of secondary causes

Diagnosis is recommended based on the 2003 Rotterdam criteria and confirmed with two of three criteria: hyperandrogenism (clinical or biochemical), irregular cycles, and polycystic ovary morphology. In adolescents, both the criteria of hyperandrogenism and irregular cycles are needed, and ovarian morphology is not included due to poor specificity. The diagnostic criteria generate four phenotypes, and clinical features are heterogeneous, with manifestations typically arising in childhood and then evolving across adolescent and adult life. Worldwide prevalence of PCOS ranges from 4% to 21% (Boyle J.A. et al, 2012) the prevalence of PCOS among different geographic regions ranges from 5% to 10% according to NIH 1990 criteria; from 10% to 15% according to the AE-PCOS 2006 criteria, and from 6% to 21% when the ESHRE/ASRM 2003 criteria were applied. (Sirmans S.M., et al, 2014) Polycystic ovary syndrome is a common (4% to 21%) disorder among reproductive age women. Depending on diagnostic criteria, PCOS's prevalence was approximately 4%–6.6% in accordance with NIH 1990 criteria and approximately 4%–21% when Rotterdam 2003 criteria were applied (Daria Lizneva, et al, 2016). In 2017, 1.55 million incident cases of PCOS among women of reproductive age (15–49 years) were reported globally, representing an increase of 4.47% (2.86–6.37%) from 2007 to 2017. The global age-standardized incidence rate of PCOS among women of reproductive age was 82.44 per 100 000 population in 2017, which represents an increase of 1.45% (1.43–1.47%) from 2007 to 2017.

There is also some evidence that women with the PCOS phenotypes A and B have an increased risk of hepatic steatosis as compared with women with PCOS with the nonhyperandrogenic phenotype and compared with healthy controls (Mehrabian F., 2011 and Jones H., et al, 2012). The highest antimüllerian hormone levels are also found in patients with classic PCOS. Most PCOS women are insulin resistant (Robinson et al., 1993; Chang et al., 2005). It is thought that insulin resistance and compensatory hyperinsulinemia are key pathological factors of PCOS (Chang RJ,et al, 1983 and Ciaraldi TP, 1992) Clinical and biochemical features of these patients may vary well according to race, ethnicity and the diagnostic criteria used (Kauffman RP, 2002). PCOS coincides with the metabolic syndrome, characterized by resistance to the action of insulin, dyslipidemia and hypertension, which is associated with increased chances for cardiovascular disease later in life (Wild, 2002). By the age of 40 years, up to 40% of all women with PCOS will have developed type II diabetes or impaired glucose tolerance (in the United States) (Dunaif, 1995). Women with PCOS have an incidence of insulin resistance of 25–70%, they would appear to be at increased risk of developing gestational diabetic complications (Legro et al., 2004)

IR also appears to play a pathogenic role in the metabolic syndrome. (Haffner SM et al, 2003) The national cholesterol education program adult treatment panel (NCEP ATP III) guidelines define the MetS as having at least three of the following abnormalities: increased waist circumference, high blood pressure, elevated fasting blood glucose, low serum high-density lipoprotein (HDL) cholesterol and hyperglycemia. (National Cholesterol Education Program, 2003)

IR also appears to play a pathogenic role in the metabolic syndrome. The national cholesterol education program adult treatment panel (NCEP ATP III) guidelines define the MetS as having at least three of the following abnormalities: increased waist circumference, high blood pressure, elevated fasting blood glucose, low serum high-density lipoprotein (HDL) cholesterol and hyperglycemia. The prevalence of PCOS among women of fertile age is 6–10% using the NIH criteria (Knochenhauer et al., 1998; Azziz et al., 2004) and 14–17% using the broader Rotterdam criteria (March et al., 2010; Tehrani et al., 2011). Obesity worsens the metabolic and endocrine profile in PCOS, and the obesity epidemic may lead to increased prevalence (Hoeger, 2006). Approximately 50% of women with PCOS are overweight or obese (Norman et al., 2004) Anti-Mullerian hormone (AMH), also known as Mullerian inhibiting substance is produced by the granulosa cells of small antral follicles (De Meyts et al., 1999; Durlinger et al., 2002; Weenen et al., 2004). AMH has an inhibiting role in the ovary, contributing to follicular arrest (Pellatt et al., 2010). AMH also correlates with the other criteria of PCOS: oligoamenorrhoea (OA) and HA (van Rooji et al., 2002; Fanchin et al., 2003; Laven et al., 2004; Eldar-Geva et al., 2005; Piltonen et al., 2005; Carlsen et al., 2009; Nardo et al., 2009; Lin et al., 2011) A meta-analysis shows that women with PCOS are at an increased risk of developing

serious complications during pregnancy, such as gestational diabetes, pregnancy-induced hypertension and pre-eclampsia. Their babies are also at greater risk of neonatal complications.

OBJECTIVES

The objectives of the study are as follows:

1. To asses clinical features and metabolic disorders in PCOS.
2. To find out relationship of PCOS with Infertility.

RATIONALE OF THE STUDY

Diagnosis of PCOS is important, because it is associated with increased risks of insulin resistance (IR), noninsulin dependent diabetes mellitus and metabolic syndrome. All of which have long-term consequences. (J Hum, 2013) Kar, S (2013) found that PCOS women have a 11-fold higher risk of having metabolic syndrome, which is a cluster of endocrine disturbances like IR, dyslipidemia, obesity, hypertension, atherosclerosis, and endothelial dysfunction (Boomsma CM, et al 2006, Barber TM et al, 2019, Ollila MM et al, 2016 and Reaven GM, 2005) PCOS is a predominant cause of infertility and a common gynae endrocrine disorder affecting 7-15% of women in reproductive age. Most of the complication of PCOS may persist lifelong. Current treatments are not avail to address all aspects of PCOS. As infertility is the devastating complication of PCOS and it is associated with other hormone, that's why this study was conducted to find out the relationship of PCOS, metabolic disorders in infertility.

MATERIALS AND METHODS:

Study area: The study was carried out in a private hospital and a government hospital at Noakhali district in Bangladesh.

Study design: It was a descriptive cross sectional study.

Sources of data: Data were collected from primary and secondary sources.

Sources of primary data: Primary data were collected from the respondents of the study areas.

Sources of data: Secondary data were collected from books, research reports, journals, different websites and internet etc.

Sampling method: Purposive and convenience sampling was followed for data collection.

Sample size: Total 100 respondents were the sample size for this study.

Tools for data collection: Questionnaire was used for data collection

Method of secondary data collection: Secondary data were collected by reviewing secondary sources of data.

Method of primary data collection: Primary data were collected by face to face interview with the respondents by using questionnaire. All women in the reproductive age group (18-45) with the primary complains of menstrual irregularities with infertility were evaluated in detail for PCOS. PCOS was diagnosed according to the 2003 Rotterdam criteria (European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) PCOS consensus workshop group) with at least two of the following three features;

(i) Oligo or anovulation
(ii) Clinical and/or biochemical hyperandrogenism, and
(iii) Ultrasound appearance of polycystic ovaries.

All participants gave written informed consent and this study was approved by our ethics committee. All anthropometric measurements were done following standard protocol and calibrated instruments by a single technician. All clinical findings like acne, obesity, hirsutism acanthosis nigricans, galactorrhea, etc., were evaluated by single gynecologist. All sonographies were performed by single gynecologist. All biochemical

and hormonal tests were carried out in the laboratory of the private hospital where this study was conducted (National hospital, Noakhali), AMH and free testosterone, which were outsourced to a standard national laboratory. Evaluation of reports and final diagnosis of PCOS was made by single gynecologist.

Oligo and anovulation was defined as: Menstrual cycles <21 days or >35 days, clinical hyperandrogenism was defined as modified Ferriman Gallway score ≥8. Biochemical hyperandrogenism as a free androgen index (FAI) of >4.5 (total testosterone, nmol/l/SHBG, nmol/l × 100). Polycystic ovary was defined as ≥12 follicles per ovary and/or ovarian volume ≥10 cm3. All participants gave fasting (>12 h) blood samples for plasma glucose, insulin, lipid profile, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), total testosterone, and SHBG. Sonography was performed in early follicular phase. Metabolic syndrome was defined according to the modified AHA/NHLBI ATP III (2005) definition. It was diagnosed if at least three of the following five features were present: 1) WC of ≥ 80 cm, 2) blood pressure of ≥130/85 mmHg, 3) fasting blood sugar of ≥100 mg/dl, 4) triglycerides of ≥150 mg/dl, and 5) high density lipoprotein (HDL) of ≤50 mg/dl.

Data analysis: Data were analyzed by using by using suitable computer program- like MS Word, Excel and SPSS.

Presentation of findings: Findings were interpreted and presented in the thesis.

RESULTS

Table 1: Age of the respondents

Age group	Frequency	Percent
15-19 Years	10	10%
20-29 Years	66	66%
30-40 Years	24	24%
Total	100	100%

Source: Field survey, 2022

Age of the respondents has shown in the above table. From the result it was found that age group 20-29 years was 66% which was maximum.

Table 2: Height of the respondents

Height (in inches)	Frequency	Percent
54	2	2%
57	2	2%
58	2	2%
59	6	6%
60	2	2%
61	26	26%
62	34	34%
63	14	14%
64	6	6%
65	6	6%
Total	100	100%

Source: Field survey, 2022

Height of the respondents has shown in the above table. From the result it was found that 34% respondents had height 62 inches which was maximum.

Table 3: Weight of the respondent

Weight (in Kg)	Frequency	Percent
51-60 Kg	8	8/%
61-70 Kg	30	30%
71-80 Kg	38	38%
81-90 Kg	16	16%
91 Kg and above	8	8%
Total	100	100%

Source: Field survey, 2022

Weight of the respondent has shown in the above table. From the result it was found that 38% respondents had 71-80 Kg weight which was maximum.

Table 4: Type of weight of the respondents

Type of weight	Frequency	Percent
Normal	8	8%
Overweight	32	32%
Obese	60	60%
Total	100	100%

Source: Field survey, 2023

Type of weight of the respondents has shown in the above table. From the result it was found that 60% respondents were obese which was maximum.

Table 5: Body Mass Index (BMI) value

BMI value	Frequency	Percent
18.5-24.9 (Normal)	8	8%
25-29.9 (Over weight)	32	32%
30-39.9 (Obesity)	54	54%
40 and above (Extreme obesity)	6	6%
Total	100	100%

Source: Field survey, 2022

BMI value of the respondents has shown in the above table. From the result it was found that 54% respondents had Obesity.

Table 6: Educational qualification of the respondents

Educational qualification	Frequency	Percent
Primary school	6	6%
Secondary	44	44%
Honours/Masters	50	50%
Total	100	100%

Source: Field survey, 2022

Educational qualification of the respondents has shown in the above table. From the result it was found that 50% respondents had Honours/Masters degree which was maximum.

Table 7: Socioeconomic status of the respondents

Socioeconomic status	Frequency	Percent
Low	12	12%
Middle	78	78%
High	10	10%
Total	50	100%

Source: Field survey, 2022

Socioeconomic status of the respondents has shown in the above table. From the result it was found that 78% respondents were from middle social class which was maximum.

Table 8: Marital status of the respondents

Marital status	Frequency	Percent
Married	100	100%
Unmarried	0	0%
Total	100	100%

Source: Field survey, 2023

Marital status of the respondents has shown in the above table. From the result it was found that all of the respondents were married as they came with the complaints of infertility.

Table 9: Fertility history

Fertility history	Frequency	Percent
Parous	34	34%
Nulliparous	66	66%
Total	100	100%

Source: Field survey, 2022

Fertility history has shown in the above table. From the result it was found that 66% respondents were Nulliparous and 34% respondents were parous.

Table 10: Type of subfertility

Type of subfertility	Frequency	Percent
Primary	66	66%
Secondary	34	34%
Total	100	100%

Source: Field survey, 2022

Type of subfertility has shown in the above table. From the result it was found that 66% respondents had primary subfertility and 34% respondents had secondary subfertility.

Table 11: Duration of subfertility (Years)

Duration of subfertility (Years)	Frequency	Percent
1-5 Years	32	32%
6-10 Years	52	52%
>10 Years	16	16%
Total	100	100%

Source: Field survey, 2022

Duration of subfertility (Years) has shown in the above table. From the result it was found that 52% respondents had 6-10 years subfertility which was maximum.

Table 12: Menstrual history of the respondents

Menstrual history	Frequency	Percent
Normal	12	12%
Reduced/Oligomenorrhoea	88	88%
Total	100	100%

Source: Field survey, 2022

Menstrual history of the respondents has shown in the above table. From the result it was found that 88% respondents had reduced menstruation /Oligomenorrhoea and only 12% respondents had normal menstruation.

Table 13: Secondary Amenorrhea

Secondary Amenorrhea	Frequency	Percent
Present	66	66%
Absent	34	34%
Total	100	100%

Source: Field survey, 2022

Secondary Amenorrhea has shown in the above table. From the result it was found that 66% respondents has secondary amenorrhea and 34% respondents had no secondary amenorrhea.

Table 14: Irregular menstruation occurs

Interval of irregular menstruation occurs	Frequency	Percent
1-3 Months interval	56	56%
3-5 months interval	44	44%
Total	100	100%

Source: Field survey, 2022

Interval of irregular menstruation occurs has shown in the above table. From the result it was found that 56% respondents replied that their irregular menstruation occur at 1-3 months interval.

Table 15: Signs of Hyperandrogenism

Signs of Hyperandrogenism	Frequency	Percent
Acne	42	42%
Acanthosis nigricans	34	34%
Hirsutism	24	24%
Multiple problem	82	82%

Source: Field survey, 2022

Signs of hyperandrogenism has shown in the above table. From the result it was found that 42% had acne and 82% respondents had more than one problem (multiple problem).

Table 16: Diet habit (healthy always)

Respondents' opinion	Frequency	Percent
Yes	32	32%
No	68	68%
Total	100	100%

Source: Field survey, 2022

Whether diet habit healthy always has shown in the above table. From the result it was found that 68% respondents had unhealthy (fast food/oily food) diet habit but only 32% respondents had healthy diet habit.

Table 17: Eating of fast food status

Respondents' opinion	Frequency	Percent
Yes	54	54%
No	46	46%
Total	100	100%

Source: Field survey, 2022

Whether respondents eat fast food or not has shown in the above table. From the result it was found that 54% respondents eat fast food but 46% respondents did not eat fast food.

Table 18: Exercise Perform by respondents

Respondents' opinion	Frequency	Percent
Yes	32	32%
No	68	68%
Total	100	100%

Source: Field survey, 2022

From the result it was found that 68% respondents did not perform exercise and 32% respondents performed exercise, but most of them were irregular in exercise.

Table 19: Serum LH: FSH status of the respondents

Serum FSH	Frequency	Percent
<2	37	37%
>2	63	63%
Total	100	100.0

Source: Field survey, 2022

Serum LH: FSH status of the respondents has shown in the above table. From the result it was found that 63% respondents had serum LH: FSH status was >2 which was significant.

Table 20: Serum Prolactin of the respondents (2-29 ng/mL)

Serum Prolactin	Frequency	Percent
<29	26	26%
>29	74	74%
Total	100	100.0

Source: Field survey, 2022

Serum Prolactin of the respondents has shown in the above table. From the result it was found that 26% respondents had normal serum prolactin value and 74% respondents had hyperprolactinemia.

Table 21: Serum AMH of the respondents

Serum AMH	Frequency	Percent
1-3.5 (Average)	8	8%
3.5-5 (Border line high)	39	39%
>5 (High)	53	53%
Total	100	100.0

Source: Field survey, 2022

Serum AMH of the respondents has shown in the above table. From the result it was found that 53% respondents had high serum AMH value.

Table 22: Impaired blood sugar of the respondents

Impaired blood sugar	Frequency	Percent
Present	34	34%
Absent	66	66%
Total	100	100%

Source: Field survey, 2023

Impaired blood sugar of the respondents has shown in the above table. From the result it was found that 66% respondents had no impaired blood sugar.

Table 23: Diabetes mellitus of the respondents

Diabetes mellitus	Frequency	Percent
Present	26	26%
Absent	74	74%
Total	100	100%

Source: Field survey, 2022

Diabetes mellitus of the respondents has shown in the above table. From the result it was found that 26% respondents had Diabetes mellitus.

Table 24: Total Cholesterol level of the respondents

Total Cholesterol level	Frequency	Percent
Normal	60	60%
High	40	40%
Total	100	100%

Source: Field survey, 2022

Total Cholesterol level of the respondents has shown in the above table. From the result it was found that 40% respondents' cholesterol level were in high condition.

Table 25: TSH (Thyroid Stimulating Hormone) of the respondents (According to American Thyroid Association)

TSH value (Miliunit/L)	Frequency	Percent
0.2-4 (Normal)	62	62%
4-10 (Hypothyroidism)	38	38%
Total	100	100.0

Source: Field survey, 2022

TSH of the respondents has shown in the above table. From the result it was found that 38% respondents had hypothyroidism.

Table 26: Testosterone status of the respondents (15-70 ng/dl) (for women)

Testosterone status	Frequency	Percent
Normal	54	54%
Increase	46	46%
Total	100	100%

Source: Field survey, 2022

Testosterone status of the respondents has shown in the above table. From the result it was found that 46% respondents had testosterone statuses were in increased condition.

Table 27: Dysmenorrhoea of the respondents

Dysmenorrhoea	Frequency	Percent
Present	28	28%
Absent	72	72%
Total	100	100%

Source: Field survey, 2022

Dysmenorrhoea of the respondents has shown in the above table. From the result it was found that 72% respondents had no Dysmenorrhoea and 28% respondents had Dysmenorrhoea.

Table 28: TVS (Transvaginal Sonography) Findings of the respondents

TVS Findings	Frequency	Percent
Normal	26	26%
PCO present	74	74%
Total	100	100%

Source: Field survey, 2022

TVS Findings of the respondents has shown in the above table. From the result it was found that 74% respondents had PCO in TVS, which was very much significant. TVS is considered the gold standard in the diagnosis of PCO.

DISCUSSION

1. Obesity: Miranda J. et al (2013) found in their study a worldwide prevalence of obesity 35% in females and up to 55% in South America and the Caribbean. Overweight and obesity have been considered a worldwide epidemic. According to the World Health Organization (WHO) (2004), they are considered eutrophics those individuals who have BMI between 18.50 and 24.99 kg/m^2, and overweight are those with a BMI between 25.00 and 29.99 kg/m^2 and obese are the ones with BMI≥30.00 kg/m^2. (Loret de Mola JR. 2009) Barber TM et al (2019) described in their study, development of PCOS, weight-gain and obesity often result in its clinical and biochemical manifestation. Accordingly, there are close links between obesity and PCOS. The majority of women with PCOS (38%-88%) are either overweight or obese. modest weight-loss (around 5%) often results in clinically meaningful improvements in the reproductive, hyperandrogenic, and metabolic features of PCOS. The World Health Organization (2000) defines obesity in adolescents as BMI $\geq 30\ kg/m^2$. However, according to criteria recommended for Asian-Pacific populations, obesity is considered a BMI $\geq 25\ kg/m^2$. Thus, studies performed in Europe or the United States defined obesity as BMI $\geq 30\ kg/m^2$, and those from the Asian-Pacific used BMI $\geq 25\ kg/m^2$. In this study it was found that 59 % patients were obese, 26% overweight and 15% normal weight. Within PCOS cases 68 % were obese, 27% overweight. Only 5% PCOS found normal weight. The effect of obesity on metabolic disorders in adolescent PCOS is likely mediated by insulin resistance (Black et al. 2013)). Hyperinsulinemia resulting from insulin resistance inhibits SHBG production in the liver, thereby increasing the availability of free androgen, which promotes obesity. Aerobic exercise can improve reproductive function in women with

PCOS, including normalizaton of menstrual cyclicity (Vigorito C, et al, 2007) and ovulation rates. (Palomba S, et al 2008) Thomson RL et al (2011) revealed in their study, exercise (possibly through improvements in insulin sensitivity) appears to result in improvements in menstrual cyclicity and/or ovulation in around 50% of women with PCOS. But this study showing that most of the patients were not aware about their health and they were relactant to do physical exercise. Only 26% patients were used to do exercise, but about half of them did it irregularly.

2. Ovulatory Dysfunction: Woolcock JG, et al (2008) Ovulatory dysfunction refers to oligomenorrhea (cycles more than 35 days apart but less than six months apart) or amenorrhea (absence of menstruation for six to 12 months after a cyclic pattern has been established) The majority of PCOS patients have ovarian dysfunction, with 70% to 80% of women with PCOS presenting with oligomenorrhoea or amenorrhoea. Among those with oligomenorrhoea, 80% to 90% will be diagnosed with PCOS (Brassard M, et al, 2008). This study observed that among PCOS patient 90% were in ovulatory dysfunction. Some of them were amenorrhoic, some suffered from Oligomennorhoea.

3. Infertility: Mascarenhas MN et al (2012) found that infertility is one of the most alarming associated morbidities in PCOS, as it currently affects approximately 48.5 million women aged 20–44 years. Infertility affects 40% of women with PCOS,and it is the most common cause of anovulatory infertility. Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. (Teede H et al, 2010) This study showing that about 82% patient having PCOS who attended with the complaints of infertility. This finding is almost similar to the study of (Teede H et al, 2010). Brassard M, et al, (2008) observed that those with PCOS and infertility, 90% are overweight. Obesity independently exacerbates infertility, reduces efficacy of infertility treatment and induces a greater risk of miscarriage. One of the main causes of anovulatory infertility is Polycystic Ovary Syndrome (PCOS) (Ben-Shlomo *et al*., 2008). This study identified that 90% of anovulatory women diagnosed having PCOS. Which is almost relevant with other studies. Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders and a major cause of anovulatory infertility in women of reproductive age (15–49 years). PCOS is the most common cause of anovulatory infertility in women (Balen *et al*., 2016). PCOS accounts for up to 70% of patients with anovulatory subfertility. Subfertility was 15-fold higher in women reporting PCOS compared with controls independent of BMI.

4. Features of Hyperandrogenism: PCOS is one of the most commonly reported endocrine and metabolic disorders among women of reproductive age. It is a heterogeneous condition characterized by features of androgen excess and ovarian dysfunction symptoms in the absence of other disease. Clinical hyperandrogenism primarily includes hirsutism, acne and male pattern alopecia (Azziz R, et al, 2006). Elevated ovarian androgen production is a core feature of PCOS and results in PCOS symptoms including hair loss, acne, oily skin, and accumulation of abdominal fat (Rosenfield & Ehrmann, 2016). Ashraf, S. et al (2019) found that Hyperandrogenism, the hallmark feature of PCOS, is clinically manifested as hirsutism, acne, and alopecia. Excessive androgen production by ovaries as well as from adrenals contributes to hyperandrogenism. Hyperandrogenemia is one of the major diagnostic features for the diagnosis of polycystic ovary syndrome (PCOS) A study showed Hyperandrogenemia was present in 78.2% of the patients. (Alexiou E, et al, 2017) Elevation of the free or total testosterone level higher than the adult female normative values is a key diagnostic feature of biochemical hyperandrogenism. Chronically elevated luteinizing hormone and insulin levels lead to increased androgen production within the ovarian theca. In this study, feature of hyperandrogenism, Hirsutism was present in 66%, Acne 59%, Acanthosis nigricans in 56% of patient. Most of the patients had one or more than one feature.Cutaneous features of hyperandrogenism in polycystic ovary syndrome (PCOS) include acne, hirsutism, seborrhea, androgenic alopecia (AGA), and acanthosis nigricans (AN)¨One study showing that, Hirsutism is the most common cutaneous finding in PCOS women.(Feng JG. Et al, 2018) this study also relevant with above findings. It reveals that hirsutism 66% in PCOs Patients as the most common criteria. Hirsutism is defined in females as male type terminal hair growth and distribution Azziz R, et al (2006). PCOS is a common cause of hirsutism occurring in approximately 60% of cases; however this varies with race and degree of obesity. One of the important etiologic factors in acne is an increase in sebaceous gland activity, which is androgen dependent. Acne is a common manifestation of hyperandrogenemia. Therefore, acne may not only cause cosmetic concern but may also be a sign of underlying disease. In females, the most common cause of hyperandrogenemia is polycystic ovary syndrome (PCOS). (Timpatanapong P and Rojanasakul A., 1997)

In this study 59% of PCOS patient had acne and 56% had acanthosisnigricans. There is a weak but significant correlation between circulatingtestosterone levels and hirsutism in women, although various circulating androgens may have stronger correlations, and many hirsute women have normal androgen levels. (Azziz R, et al, 1998) The present data indicate that determination of free T provides little additional information in the diagnosis of hirsutism or PCOS and does not have to be included to the basic evaluation of these patients. Only half of women with PCOS exhibited elevated serum free Testeron concentrations. (Penttilä TA, et al, 1996) In this study, it was found that 51% had increased prolactin level in PCOS patients, that was very much significant. Other causes of hyperproactinemia were excluded and only one patient found to had pituitary adenoma.

5. Metabolic Disorder: The prevalence of the metabolic syndrome defined as obesity, hypertension, dyslipidemia, and hyperglycemia is approximately threefold higher in women with PCOS. (Moran Lj. et al 2010) Androgen excess plays a prominent role in the development of metabolic disturbances associated with PCOS, with a discernible impact on key peripheral metabolic tissues, including the adipose, liver, pancreas, and muscle, and very prominently the brain, contributing to the constellation of metabolic complications of PCOS, from obesity to insulin resistance. (Sanchez-Garrido MA and Tena-Sempere, M 2020) PCOS is closely linked to metabolic disorders such as obesity and insulin resistance (IR). (Gilbert E.W. et al, 2018) A large proportion of women with PCOS are obese or overweight (Moran C., et al, 2012) and exhibit IR with associated compensatory hyperinsulinemia (Legro R.S., et al, 2004) Of note, IR and hyperinsulinemia are metabolic traits that are also present in most lean women with PCOS. Hyperinsulinemia plays a prominent role in the development of some phenotypic features of PCOS and, together with β cell dysfunction, increases the risk of developing other metabolic abnormalities such as type 2 diabetes (T2D), hypertension, dyslipidemia, and cardiovascular diseases. (Bednarska S. and Siejka A., 2017) Importantly, the prevalence of these metabolic comorbidities is high in women with this disorder (Moran L.J., et al, 2010) and the concurrence of overweight or obesity and PCOS exacerbates not only metabolic complications , but also reproductive derangements associated with this endocrinopathy (Rojas J., et al, 2014) This study reveals that 24% PCOS patients had DM, 46% PCOS patients had impaired glucose tolerance. Almost all of these patients were obese or overweight. It indicates that obesity exacerbate metabolic complications. These findings are relevant to so many previous study and meta analysis. Hyperandrogenism plays a prominent role in the development of metabolic disturbances associated with PCOS, acting on peripheral tissues as well as at the central level

6. Insulin Resistance: Sultan C, Paris F. (2006) revealed that insulin resistance, hyperinsulinemia, and obesity are commonly identified in women with PCOS. However, with the exception of a single publication, none of the current definitions, recommendations, or guidelines includes IR and/or hyperinsulinemia as a diagnostic feature. Metabolic syndrome is twice as common in patients with polycystic ovary syndrome compared with the general population, and patients with polycystic ovary syndrome are four times more likely than the general population to develop type 2 diabetes mellitus. Insulin resistance affects nearly all women with PCOS. Some experts say 70% while others would argue it affects all women with PCOS to some degree. Some research indicates there may be a gene that is turned on by environmental factors. Insulin Resistance left untreated will lead to diabetes and higher chances of heart disease. Insulin resistance is a complex condition in which body does not respond as it should to insulin that's essential for regulating blood sugar levels. Several genetic and lifestyle factors can contribute to insulin resistance. One theory maintains that underlying insulin resistance exacerbates hyperandrogenism by suppressing synthesis of sex hormone binding globulin and increasing adrenal and ovarian synthesis of androgens, thereby increasing androgen levels. These androgens then lead to irregular menses and physical manifestations of hyperandrogenism. (DeUgarte CM, et al, 2005) IR may be present in PCOS independently of obesity. IR, defined as a metabolic state characterized by a decrease in cellular ability to respond to insulin signaling, appears to be an essential pathophysiologic mechanism in the development of all metabolic complications of PCOS (Apridonidze T, et al, 2005). Hyperinsulinemia leads to increased androgen production, which, in turn, may impair insulin sensitivity. This vicious cycle induces and worsens the reproductive and metabolic abnormalities that characterize PCOS. (Moghetti P., and Tosi F., 2021) Weight-gain and obesity in women with PCOS also promote worsening insulin resistance and both metabolic dysfunction (mediated through further impairment of the PI3-kinase post-receptor insulin pathway) and the characteristic reproductive and hyperandrogenic features of this condition. (Barber TM, et al, 2006) Women with PCOS have intrinsic IR independent of the extent of obesity and magnitude of androgen concentrations (Dunaif A, et al, 1989) The

presence of PCOS is also associated with a fourfold increase in the risk of type 2 diabetes mellitus (Celik C, et al, 2014)

Even lean women with PCOS manifest IR; increasing body mass index (BMI) exacerbates IR. Normal-weight adolescent girls with PCOS have peripheral IR, increased liver fat, and muscle mitochondrial dysfunction compared with normal-weight girls. (Cree-Green M, et al, 2017) The majority of women with PCOS (50%-90%) are insulin resistant. Weight-gain and obesity worsen insulin resistance and features of the metabolic syndrome. (Gerald M Reaven, 2005) This finding revealed that all diabetic PCOS patients were obese. Most of the overweight patients had insulin resistance that is relevant to Gerald study findings. Women with PCOS have a four-fold increased risk of developing gestational diabetes compared with the reference group of pregnant women without PCOS. Moreover, the children born from mothers diagnosed with PCOS seem nearly 4 times more often small for gestational age. (De Wilde, M. A., et al, 2017)

Obesity increases insulin resistance and the resulting hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity also sensitizes thecal cells to luteinizing hormone (LH) stimulation, resulting in functional ovarian hyperandrogenism. Moreover, obesity affects inflammatory adipokines, which, in turn, increases insulin resistance and adipogenesis. (Glueck CJ and Goldenberg N., 2019) (Moran LJ et al 2010) described that women with PCOS had increased prevalence of impaired glucose tolerance and DM2 independently of BMI. In a Danish registry study, the risk of DM2 was 4 times greater among women with PCOS. Furthermore, DM2 was diagnosed 4years earlier in women with PCOS compared with unaffected control women. (Rubin KH et al, 2017) Legro RS et al (1999) found that PCOS is associated with impaired glucose tolerance in up to 30% and DM2 in up to 10% of women with PCOS. In this study, among PCOS patient it was found 26% cases had diabetes mellitus and 44 % had insulin resistance. Obesity has profound effects on sex hormone secretion and metabolism resulting in changes to the bioavailability of oestrogen and androgens. With increasing adiposity, there is an increase in peripheral aromatisation of androgens to oestrogens with a concurrent decease in the hepatic synthesis of sex hormone-binding globulin (SHBG). This results in an increase in free oestradiol and testosterone levels. This is further exacerbated by an associated hyperinsulinaemia

7. Lipid Profile: Wild R.A. et al (1985) found that PCOS may represent an important model of lipid alterations starting during adolescence or fertile age. In fact, dyslipidemia is common in young adult women with PCOS. This disorder may be the most common cause of dyslipidemia in women before the age of 40 years. Although low-density lipoprotein cholesterol (LDL-C) is considered to be the primary target to reduce CVD, prevalent metabolic syndrome in women with PCOS. (Apridonidze T. et al, 2005) However, during past decade, a large number of studies have found an increase of LDL-C levels in women with PCOS. (Wild R.A., et al, 1992) Therefore, recently both the American College of Obstetricians and Gynecologists (ACOG) and the Androgen Excess and PCOS Society guidelines have recommended that women with PCOS should have a complete fasting lipid and lipoprotein evaluation as part of their cardiovascular risk assessment. Metabolic syndrome is a collection of symptoms with higher risk for chronic diseases such as diabetes, heart disease, and cancer. At least 2 criteria are needed to diagnose metabolic syndrome. The criteria are:
High blood pressure.
1. High abdominal: waist ratio or central obesity of greater than 40 inches.
2. HDL or good cholesterol lower than 40mg/dl for men, 50mg/dl for women.
3. Triglycerides greater than 150mg/dl.

A meta-analyses including 30 studies with the mean age of women <45 years found higher mean serum low density lipoprotein, LDL, cholesterol, LDL-C, non high density lipoprotein HDL and triglyceride TG levels in women with PCOS compared with control women. (Wild RA, et al, 2011) Dyslipidemia is common in PCOS. Beyond known alterations in triglycerides and HDL-cholesterol, women with PCOS have higher LDL-cholesterol and nonHDL-cholesterol, regardless of BMI (Wild RA, et al, 2010). They recommended that all women with PCOS be screened for dyslipidemia, including LDL-cholesterol and non HDL-cholesterol determinations, for effective cardiovascular risk prevention. This study revealed that, 41% PCOS patients had high triglyceride level, about 34% altered LDL and HDL level, 24% had raised blood pressure. That means dyslipidemia is common in PCOS patients, similar findings with other studies.

8. Lutenizing Hormone (LH) and Follicle Stimulating Hormone (FSH): Lutenizing Hormone (LH) and Follicle Stimulating Hormone (FSH): LH and FSH are hormones that encourage a woman's body to ovulate and are both secreted by the pituitary gland. Low or imbalanced levels of these hormones cause both infertility and irregular periods. LH and FSH pulse frequencies are modulated by GnRH pulse frequency. Increased GnRH pulse frequency increases LH pulse frequency and decreases FSH pulse frequency (Wildt L, et al, 1981) Women with PCOS demonstrate increased frequencies and amplitudes of GnRH and LH pulses, increased LH levels, reduced FSH and an increased LH to FSH ratio, and a reduced capacity to mount the LH surge that initiates ovulation (Chang & Cook-Andersen, 2014; Chen et al., 2015; Coyle & Campbell, 2019; McCartney & Campbell, 2020). Altered LH-FSH dynamics, combined with elevated ovarian androgens, contribute to the follicular arrest, anovulation, and cyst formation characteristic of PCOS (Franks & Hardy, 2020). Elevated ovarian androgen production is a core feature of PCOS and results in PCOS symptoms including hair loss, acne, oily skin, and accumulation of abdominal fat (Rosenfield & Ehrmann, 2016). In this study, it was found that 63 % patients having altered LH, FSH ratio. LH/FSH > 2 is significant. All of these patients diagnosed as PCOS at last.

9. Anti Mullrian Hormone (AMH): In women with PCOS, elevated levels of AMH appear to play an important role in long term disruption of ovarian physiology, with greater AMH concentrations being linked to worse fertility outcomes (Pierre A, et al, 2013) Pigny P, et al (2003) found that AMH concentrations are often elevated in women with PCOS. AMH concentrations reflect ovarian reserve and are correlated with the number of growing follicles. AMH concentrations were found to be higher in girls with obesity with PCOS compared to girls with obesity without PCOS of comparable age and pubertal status (Kim JY, et al, 2017) in this study, AMH level is high in 66% PCOS patient. This finding is significant. The characteristic arrest of antral follicular development in PCOS results in high AMH (Zhao, Y. et al., 2019). AMH levels are higher in anovulatory compared to ovulatory women with PCOS (Cimino et al., 2016)

10. Prolactin: PRL levels in patients who were diagnosed according to the Rotterdam criteria were significantly higher than non-PCOS participants. Slightly higher levels of PRL could be presented as a diagnostic feature of PCOS. (Saei Ghare Naz M, et al, 2022) Melmed, S.; et al (2011) found that hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis and has a prevalence of approximately 90 per 100,000 women. The Endocrine Society Clinical Practice Guideline has categorized PCOS as an etiology of hyperprolactinemia, as 3–67% of women with PCOS suffer from hyperprolactinemia. (Delcour, C.; et al, 2019) In this study % had hyperprolactatinemia.

11. TVS (Transvaginal sonography): A polycystic ovary is defined as an ovary containing 12 or more follicles (or 25 or more follicles using new ultrasound technology) measuring 2 to 9 mm in diameter or an ovary that has a volume of greater than 10 mL on ultrasonography. A single ovary meeting either or both of these definitions is sufficient for diagnosis of polycystic ovaries. Polycystic ovary morphology (PCOM) is enlarged ovaries with increased stroma and more small peripheral cysts. The Androgen Excess–PCOS Society Task Force recommended that PCOM is defined as ≥20 follicles per ovary using a transvaginal probe and high-resolution technology (transducer frequency ≥8 MHz) (Dewailly D, et al, 2014). In this study 85% PCOS patients having polycystic ovary in TVS. It's reflecting that TVS is an important diagnostic tool.

12. DIET: Harrison CL, et al (2011) found that lifestyle modification and weight reduction reduce insulin resistance and can significantly improve ovulation. Therefore, lifestyle modification is first-line therapy for women who are overweight. A calorie-restricted diet is recommended for all patients with PCOS who are overweight. Weight loss has been shown to have a positive effect on fertility and metabolic profile. (Costello M, et al, 2007) A low-energy diet compared with a healthy diet for 6 months was associated with weight loss, more regular menses, and decreased hirsutism (Marzouk TM and Sayed Ahmed WA., 2015). In this study it revealed that about 90 % patient was used to intake high calorie diet and only 26% patient had habit of exercise. Fast food is now a days in choice list of many patients. PCOS is characterized by excessive ovarian and/or adrenal androgen secretion. Intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production. Characteristic features include more growing follicles in women with PCOS compared with normal controls with premature growth arrest of antral follicles at 5 to 8 mm. (Pache TD and Fauser BC, 1993)

CONCLUSION

All of the study populations were infertile and most of them were overweight or obese. Oligomenorrhoea, amenorrhoea, hirsutism, acne, were common features in these patients. More than half of cases had LH/FSH ratio >2. Positive correlation was found among increased BMI, increased LH/FSH ratio, serum testosterone, serum TSH, fasting blood sugar, fasting insulin and insulin resistance. Significant number of PCOS patients had increased AMH level and majority had polycystic changes in ovaries. As there are wide variations in presentation and hormonal and metabolic characteristics in these patients further larger multicentic studies can be undertaken to determine the clinical and metabolic behavior of Bangladeshi women with PCOS. Further studies are required to identify the more information about pathophysiology of PCOS and the relationships between IR, hyperinsulinemia, and hyperandrogenism, obesity.

More studies are required to find out appropriate treatment guideline Proper management of obesity and IR will improve the quality of life and especially their fertility outcomes, which are often the main concern of both patients and physicians in the management of this pathology.

REFERENCES

1. Alexiou E, Hatziagelaki E, Pergialiotis V, Chrelias C, Kassanos D, Siristatidis C, Kyrkou G, Kreatsa M, Trakakis E. Hyperandrogenemia in women with polycystic ovary syndrome: prevalence, characteristics and association with body mass index. Horm Mol Biol Clin Investig. 2017 Mar 1; 29(3):105-111. doi: 10.1515/hmbci-2016-0047. PMID: 28099123.
2. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism.* 2005; 90 (4):1929–1935.
3. Ashraf, S., Nabi, M., Rasool, S.u.A. *et al.* Hyperandrogenism in polycystic ovarian syndrome and role of *CYP* gene variants: a review. *Egypt J Med Hum Genet* 20, 25 (2019). https://doi.org/10.1186/s43042-019-0031-4.
4. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. Androgen Excess Society. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab.* 2006; 91:4237–4245. doi: 10.1210/jc.2006-0178.
5. Azziz R,Waggoner WT, Ochoa T, Knochenhauer ES, Boots LR 1998 Idiopathic hirsutism: an uncommon cause of hirsutism in Alabama. *Fertil Steril* 70:274–278
6. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener-Victorin E, Fauser BC, Norman RJ, Teede H. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016 Nov; 22(6):687-708. doi: 10.1093/humupd/dmw025. Epub 2016 Aug 10. PMID: 27511809.
7. Barber TM, Hanson P, Weickert MO, Franks S. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. Clin Med Insights Reprod Health. 2019 Sep 9;13: 1179558119874042.
8. Barber TM, McCarthy MI, Wass JA, Franks S. Obesity and polycystic ovary syndrome. Clin Endocrinol (Oxf). 2006 Aug; 65(2):137-45. doi: 10.1111/j.1365-2265.2006.02587.x. PMID: 16886951.
9. Bednarska S., Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: what's new? *Advances in Clinical and Experimental Medicine.* 2017; 26(2):359–367.
10. Ben-Shlomo I, Grinbaum E, Levinger U. Obesity-associated infertility - the earliest known description. Reprod Biomed. 2008; 17:5–6.
11. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006 Nov-Dec; 12(6):673-83. doi: 10.1093/humupd/dml036. Epub 2006 Aug 4. PMID: 16891296.
12. Boyle J.A. Cunningham J. O'Dea K. Dunbar T.Norman R.J. Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. *Med Clin North Am.* 2012; 92:1163–1192.
13. Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. Med Clin North Am. 2008;92:1163–1192. doi: 10.1016/j.mcna.2008.04.008. xi.
14. Celik C, Tasdemir N, Abali R, Bastu E, Yilmaz M. Progression to impaired glucose tolerance or type 2 diabetes mellitus in polycystic ovary syndrome: a controlled follow-up study. *Fertil Steril.* 2014; 101(4):1123-1128.e1.

15. Chang RJ, Nakamura RM, Judd HL, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J ClinEndocrinolMetab. 1983; 57(2):356–9.
16. Chen, J. , Shen, S. , Tan, Y. , Xia, D. , Xia, Y. , Cao, Y. , Wang, W. , Wu, X. , Wang, H. , Yi, L. , Gao, Q., & Wang, Y. (2015). The correlation of aromatase activity and obesity in women with or without polycystic ovary syndrome. Journal of Ovarian Research, 8, 4–9. 10.1186/s13048-015-0139-1.
17. Ciaraldi TP, El Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J ClinEndocrinolMetab. 1992;75(2):577–83.
18. Cimino, I. , Casoni, F. , Liu, X. , Messina, A. , Parkash, J. , Jamin, S. P. , Catteau-Jonard, S. , Collier, F. , Baroncini, M. , Dewailly, D. , Pigny, P. , Prescott, M. , Campbell, R. , Herbison, A. E. , Prevot, V. , & Giacobini, P. (2016). Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion. Nature Communications, 7, 1–12. 3
19. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2007;1:CD005552.
20. Coyle, C., & Campbell, R. E. (2019). Pathological pulses in PCOS. Molecular & Cellular Endocrinology, 498, 110561.
21. Cree-Green M, Rahat H, Newcomer BR, Bergman BC, Brown MS, Coe GV, Newnes L, Garcia-Reyes Y, Bacon S, Thurston JE, Pyle L, Scherzinger A, Nadeau KJ. Insulin resistance, hyperinsulinemia, and mitochondria dysfunction in nonobese girls with polycystic ovarian syndrome. *J Endocr Soc*. 2017; 1(7):931–944.
22. Daria Lizneva, M.D., Ph.D Larisa Suturina, M.D., Ph.D.Walidah Walker, M.P.H.SoumiaBrakta, M.D.Larisa Gavrilova-Jordan, M.D.Ricardo Azziz, M.D., M.P.H., M.B.A. VOLUME 106, ISSUE 1, P6-15, JULY 01, 2016 Criteria, prevalence, and phenotypes of polycystic ovary syndrome Published: May 24, 2016
23. De Wilde, M. A., Lamain-de Ruiter, M., Veltman-Verhulst, S. M., Kwee, A., Laven, J. S., Lambalk, C. B., Eijkemans, M. J. C., Franx, A., Fauser, B. C. J. M., & Koster, M. P. H. (2017). Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype. *Fertility and Sterility*, *108*(2),333-340.
24. Delcour, C.; Robin, G.; Young, J.; Dewailly, D. PCOS and Hyperprolactinemia: What do we know in 2019? Clin. Med. Insights Reprod. Health 2019, 13, 1179558119871921.
25. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. *Fertil Steril.* 2005;83(5):1454-1460.
26. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. *Hum Reprod Update*. 2014; 20(3):334–352.
27. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*. 1989;38(9):1165–1174.
28. Feng JG, Guo Y, Ma LA, Xing J, Sun RF, Zhu W. Prevalence of dermatologic manifestations and metabolic biomarkers in women with polycystic ovary syndrome in north China. J Cosmet Dermatol. 2018 Jun; 17(3):511-517. doi: 10.1111/jocd.12387. Epub 2017 Sep 21. PMID: 28940857.
29. Franks S. Polycystic ovary syndrome: a changing perspective. Clin Endocrinol (Oxf) 1989;31:87–120.
30. Gerald M Reaven, The Metabolic Syndrome: Requiescat in Pace, *Clinical Chemistry*, Volume 51, Issue 6, 1 June 2005, Pages 931–938, https://doi.org/10.1373/clinchem.2005.048611
31. Giallauria F, Palomba S, Vigorito C, Tafuri MG, Colao A, Lombardi G, Orio F. Androgens in polycystic ovary syndrome: the role of exercise and diet. Semin Reprod Med. 2009 Jul;27(4):306-15. doi: 10.1055/s-0029-1225258. Epub 2009 Jun 15. PMID: 19530064.
32. Gilbert E.W., Tay C.T., Hiam D.S., Teede H., Moran L.J. Comorbidities and complications of polycystic ovary syndrome: an overview of systematic reviews. *Clinical Endocrinology (Oxf)* 2018
33. Glueck CJ, Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism. 2019 Mar; 92:108-120. doi: 10.1016/j.metabol.2018.11.002. Epub 2018 Nov 13. PMID: 30445140.
34. Haffner SM, D'Agostino R, Jr, Festa A, Bergman RN, Mykkanen L, Karter A, et al. Low insulin sensitivity (S(i) = 0) in diabetic and nondiabetic subjects in the insulin resistance atherosclerosis study: is it associated with components of the metabolic syndrome and nontraditional risk factors? Diabetes Care. 2003; 26(10):2796–803.

35. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. *Hum Reprod Update.* 2011; 17(2):171-183.
36. J Hum Reprod Anthropometric, clinical, and metabolic comparisons of the four Rotterdam PCOS phenotypes: A prospective study of PCOS women Sci. 2013 Jul-Sep; 6(3): 194–200.doi: 10.4103/0974-1208.121422.
37. Jones H. Sprung V.S. Pugh C.J. Daousi C. Irwin A. Aziz N. et al. Polycystic ovary syndrome with hyperandrogenism is characterized by an increased risk of hepatic steatosis compared to nonhyperandrogenic PCOS phenotypes and healthy controls, independent of obesity and insulin resistance. *J Clin Endocrinol Metab.* 2012; 97: 3709-3716.
38. Kauffman RP, Baker VM, Dimarino P, Gimpel T, Castracane VD. Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations. Am J Obstet Gynecol. 2002; 187(5):1362–9.
39. Kim JY, Tfayli H, Michaliszyn SF, Lee S, Nasr A, Arslanian S. Anti-Müllerian hormone in obese adolescent girls with polycystic ovary syndrome. *J Adolesc Health*. 2017; 60(3):333–339.
40. Legro R.S., Castracane V.D., Kauffman R.P. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. *Obstetrical and Gynecological Survey.* 2004; 59 (2):141–154.
41. Legro RS, Kunselman AR, Dodson WC, et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999; 84: 165–169.
42. Legro RS. Obesity and PCOS: implications for diagnosis and treatment. Semin Reprod Med. 2012 Dec; 30 (6):496-506. doi: 10.1055/s-0032-1328878. Epub 2012 Oct 16. PMID: 23074008; PMCID: PMC3649566.
43. Loret de Mola JR. Obesity and Its Relationship to Infertility in Men and Women. *Obstet Gynecol Clin North Am.* 2009; 36:333–346.
44. Marzouk TM, Sayed Ahmed WA. Effect of dietary weight loss on menstrual regularity in obese young adult women with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol*. 2015; 28(6):457–461.
45. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Medicine. 2012;9(12)e1001356
46. McCartney, C. R., & Campbell, R. E. (2020). Abnormal GnRH pulsatility in polycystic ovary syndrome: Recent insights. Current Opinion in Endocrine & Metabolic Research, 12, 78–84. 10.1016/j.coemr.2020.04.005
47. Mehrabian F. Khani B. Kelishadi R Kermani N. The prevalence of metabolic syndrome and insulin resistance according to the phenotypic subgroups of polycystic ovary syndrome in a representative sample of Iranian females. *J Res Med Sci.* 2011; 16: 763-769.
48. Melmed, S.; Casanueva, F.F.; Hoffman, A.R.; Kleinberg, D.L.; Montori, V.M.; Schlechte, J.A.; Wass, J.A. Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011, *96*, 273–288.
49. Miranda J, Herrero V, Chirinos J, et al. Major cardiovascular risk factors in Latin America: a comparison with the United States: the Latin American consortium of studies in obesity (LASO) *PLoS ONE*. 2013;8(1)e54056.
50. Moghetti P., Insulin resistance and PCOS: Chicken or egg? *J. Endocrinol. Investig.* 2021;44:233–244. doi: 10.1007/s40618-020-01351-0.
51. Moran C., Arriaga M., Rodriguez G., Moran S. Obesity differentially affects phenotypes of polycystic ovary syndrome. *The Internet Journal of Endocrinology.* 2012:317241. 2012.
52. Moran L. Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod Update.* 2009; 15: 477-488.
53. Moran L.J., Misso M.L., Wild R.A., Norman R.J. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Human Reproduction Update.* 2010; 16(4):347–363.
54. National Institutes of Health. Evidence-based methodology workshop on polycystic ovary syndrome, December 3-5, 2012. Accessed March 1, 2016.
55. Ollila MM, Piltonen T, Puukka K, Ruokonen A, Järvelin MR, Tapanainen JS, Franks S, Morin-Papunen L. Weight Gain and Dyslipidemia in Early Adulthood Associate With Polycystic Ovary Syndrome: Prospective Cohort Study. J Clin Endocrinol Metab. 2016 Feb;101(2):739-47. doi: 10.1210/jc.2015-3543. Epub 2015 Dec 10. PMID: 26652764.

56. Pache TD, Fauser BC. Polycystic ovaries in female-to-male transsexuals. *Clin Endocrinol (Oxf)*. 1993; 39(6):702–703.
57. Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, Colao A, Vigorito C, Zullo F, Orio F. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod. 2008 Mar; 23(3):642-50. doi: 10.1093/humrep/dem391. Epub 2007 Dec 23. PMID: 18158291.
58. Penttilä TA, Anttila L, Törmä A, Koskinen P, Erkkola R, Irjala K. Serum free testosterone in polycystic ovary syndrome measured with a new reference method. Fertil Steril. 1996 Jan; 65 (1):55-60. doi: 10.1016/s0015-0282(16)58027-3. PMID: 8557155.
59. Pierre A, Peigné M, Grynberg M, et al. Loss of LH-induced down-regulation of anti-Mullerian hormone receptor expression may contribute to anovulation in women with polycystic ovary syndrome. Human Reproduction. 2013; 28(3):762–769.
60. Pigny P, Merlen E, Robert Y, Cortet-Rudelli C, Decanter C, Jonard S, Dewailly D. Elevated serum level of anti-Mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. *J Clin Endocrinol Metab*. 2003; 88(12):5957–5962.
61. Reaven GM. The metabolic syndrome: requiescat in pace. Clin Chem. 2005 Jun; 51(6):931-8. doi: 10.1373/clinchem.2005.048611. Epub 2005 Mar 3. PMID: 15746300.
62. Rojas J., Chavez M., Olivar L., Rojas M., Morillo J., Mejias J. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. *International Journal of Reproductive Medicine.* 2014; 2014:719050.
63. Rosenfield, R. L., & Ehrmann, D. A. (2016). The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine Reviews*, 37(5), 467–520.
64. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004; 19: 41-47.
65. 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.
66. Rubin KH, Glintborg D, Nybo M, et al. Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2017; 102: 3848–3857.
67. Saei Ghare Naz M, Mousavi M, Mahboobifard F, Niknam A, Ramezani Tehrani F. A Meta-Analysis of Observational Studies on Prolactin Levels in Women with Polycystic Ovary Syndrome. Diagnostics. 2022; 12(12):2924.
68. Sanchez-Garrido MA, Tena-Sempere M. Metabolic dysfunction in polycystic ovary syndrome: Pathogenic role of androgen excess and potential therapeutic strategies. Mol Metab. 2020 May; 35:100937. Doi: 10.1016/j.molmet.2020.01.001. Epub 2020 Feb 5. PMID: 32244180; PMCID: PMC7115104.
69. Sirmans S.M. Parish R.C. Blake S.Wang X. Epidemiology and comorbidities of polycystic ovary syndrome in an indigent population. *J Investig Med.* 2014; 62: 868-874.
70. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impact on health across the lifespan. BMC Med. 2010; 8:41.
71. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106(25):3143–421.
72. Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obes Rev. 2011 May; 12(5):e202-10. doi: 10.1111/j.1467-789X.2010.00758.x. PMID: 20546140.
73. Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol. 1997 Apr; 24(4):223-9. doi: 10.1111/j.1346-8138.1997.tb02778.x. PMID: 9164062.
74. Wild R.A. Painter P.C.Coulson P.B.Carruth K.B.Ranney G.B.Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome.J Clin Endocrinol Metab. 1985; 61: 946-951.
75. Wild R.A., Alaupovic P.Parker I.J.Lipid and apolipoprotein abnormalities in hirsute women. I. The association with insulin resistance. Am J Obstet Gynecol. 1992; 166: 1191-1196.

76. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2011 Mar 1; 95(3):1073-9.e1-11. doi: 10.1016/j.fertnstert.2010.12.027. Epub 2011 Jan 17. PMID: 21247558.
77. Wildt L, Häusler A, Marshall G, Hutchison JS, Plant TM, Belchetz PE, Knobil E. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinology. 1981; 109(2):376–385.
78. Woolcock JG, Critchley HO, Munro MG, Broder MS, Fraser IS. Review of the confusion in current and historical terminology and definitions for disturbances of menstrual bleeding. *Fertil Steril.* 2008; 90 (6):22
79. Zhao, Y., Wang, C., Liang, Z., & Liu, X. (2019). Diagnostic value of anti-Müllerian hormone as a biomarker for polycystic ovary syndrome: A meta-analysis update. *Endocrine Practice*, 25(10), 1056–1066.