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Evaluation of spectrum of clinical presentation and role of Amh in women with PCOS attending the Gynae-Obs Opd of a tertiary care hospital

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SUMMARY

Background: Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects reproductive females worldwide and has 10% prevalence. The major endocrine disruption is hyperandrogenism, oligo-anovulation and some women may also have abnormal insulin activity.1 Various body systems are affected by polycystic ovarian syndrome which results in health complications like menstrual dysfunction, hirsutism, acne, obesity, and metabolic syndrome.

Aim: This study emphasizes on evaluating the spectrum of clinical presentation of PCOS and Role of AMH in women with PCOS attending the Gynae-Obs Out-patient department of a tertiary care hospital.

Methodology: A prospective observational study was carried out in the Gynecology & Obstetrics OPD at SMI Hospital, Dehradun. A self-designed questionnaire-based study was conducted on subjects with symptoms of Polycystic Ovarian Syndrome.

Data collection: The data collected included: Demographic details, Family History, Gynecological History, Clinical features, Personal Habits. Microsoft Excel and SPSS 25 software was used for the calculations.

Results: The incidence rate of PCOS, the mean age of women diagnosed with PCOS and mean of menarche were calculated. It was found that 20% of PCOS women were obese and had a BMI above 30 kg/m^2. 37% of PCOS women were overweight and had a BMI between 25.1-29.9 kg/m^2. Global Acne Scoring Method and Ferriman-Galleway method were used to assess occurrence of acne and hirsutism. Part from the spectrum of clinical presentation, the emerging role of AMH in PCOS was also evaluated. SPSS 25 software was used for statistical analysis for evaluating the effects of risk factors associated with PCOS on Serum AMH levels. Chi-square tests were used for the assessment of co-relation among these factors. P-value <0.05 was considered significant. The risk factors that were significant to AMH levels were Duration of period cycle, Flow in menses, History of DM, thyroid issues and hypertension, Family history of DM, hypertension, thyroid issues, Gynecological history of mother and sisters, and BMI.

Conclusion: In conclusion, the present study suggests that PCOS is an emerging health concern among reproductive women and is associated with many consequences like menstrual irregularities, hirsutism, acne, alopecia, and infertility, which were common endocrine disorders. Family history of diabetes and hypothyroidism were important risk factors associated with PCOS. Women who were overweight/obese were at a higher risk of developing PCOS. History of menstrual irregularities and PCOD/PCOS in mother and sisters of women also had significance in the occurrence of PCOS. AMH levels will provide reliable information in diagnosing PCOS and should be used in future along with Rotterdam or NIH criteria.

Keywords: Bariatric; Surgery; COVID-19

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INTRODUCTION

Antibiotics Polycystic ovarian syndrome (PCOS) is an endocrine disorder that affects reproductive females worldwide and has a 10% prevalence. The major endocrine disruption is hyperandrogenism, oligo-anovulation and some women may also have abnormal insulin activity. [1]. Various body systems are affected by polycystic ovarian syndrome which results in health complications like menstrual dysfunction, hirsutism, acne, obesity, and metabolic syndrom [1]. PCOS also characterizes a risk of dyslipidemia, Type-II diabetes, and cardiovascular disease. There is a variable degree of expression in every case which is why it is referred to as a Syndrome and not a disease. [2] the most common risk factors associated with PCOS are obesity, diabetes mellitus, thyroid issues, high intake of fatty foods, lack of physical exercise, and family history of diabetes, hypertension, thyroid, PCOD, and other menstrual cycle irregularity disorders. In 2004, Rotterdam established a diagnostic -criteria for PCOS, according to which there should be a presence of at least two of the following characteristics:

- Chronic anovulation
- Hyperandrogenism
- Polycystic ovaries on ultrasonography

In the pathophysiology of PCOS, the most common finding is ovarian dysfunction. This ovarian dysfunction is strongly affected by alteration in the Gonadotropin-releasing hormone. This causes an increase in the Luteinising hormone (LH), which in turn causes hyperandrogenism, and infertility [3]. Alteration in insulin resistance leads to increased insulin production, called hyperinsulinemia, which might lead to complications like Diabetes mellitus and exaggerates symptoms of PCOS. Environmental factors and lifestyle also play an important role in the pathophysiology of PCOS3.

CLINICAL PRESENTATION AND SYMPTOMATOLOGY

The symptoms of PCOS include:

Menstrual irregularity: As compared to non-PCOS women, women who have PCOS have irregular menstrual cycles. This leads to oligomenorrhea, hypomenorrhea, dysmenorrhea and, amenorrhea. [4]

Hirsutism: Hirsutism is defined as the excessive terminal hair growth that usually takes up a male pattern distribution. Hairs cover the entire surface of the human body, except for the lips, palms of the hands, and soles of the feet [2].

Oily Skin & Acne: Women with PCOS have complaints of acne in areas of cheeks, chin, chest, forehead, and back due to hormonal imbalances [4-13].

Alopecia: Due to hormonal imbalances, several women with PCOS presents with hair fall issues that are more than norma [14].

Weight gain: Sudden weight gain in PCOS women is an important clinical finding[4].

Role of Anti-Mullerian Hormone in the pathophysiology of PCOS:The ovarian follicle consists of the oocytes which are responsible for the reproductive function in women. With age, the size of the ovarian follicle and the number of oocytes decreases, causing a decrease in the ovarian reserve [7]. The ovarian follicle is developed at the fetal age, with about a million oocytes present at the time of birth. The number decreases during childhood and at menarche, there are about 3-5 lac oocytes present [7]. From the follicle pool, they enter into the growing pool with the help of FSH. From this growing pool, only one follicle becomes dominant and ovulates under the LH influence. This process continues till menopause when all the follicles are exhausted [7,8]. For the assessment of ovarian reserve in an individual, serum FSH is measured by assessing the inhibin B and E2 concentrations, which are produced in response to FSH7. These serum values have relative changes according to reproductive age and are not independent of each other. So far ultrasonography best predicts the Antral Follicle Count in the ovaries but is not feasible all the time, so a serum marker is required for this and Anti-Mullerian hormone does the job effectively [9,10]. An Anti-Mullerian hormone is produced by the cells of the antral follicles and its levels can be assessed in the serum [7]. AMH levels can be used for determining ovarian aging. It is exclusively secreted by the growing follicles, so it gives an indirect measurement of the follicle pool. Since elevated FSH levels are not detected in the serum till the cycles become irregular, so serum AMH values are more reliable [7,6,10].

In conditions like PCOS, serum AMH levels can provide information on ovarian pathophysiology. In PCOS, there is a disruption in the selection of a dominant follicle to be ovulated, which results in anovulation [7,8]. As a result of this, several small growing follicles produce AMH, and so AMH levels are increased in women suffering from polycystic ovaries. Sometimes, there is a small number of follicles present that are not detected in ultrasonography, but they contribute to the secretion of AMH, which is why serum AMH levels are elevated giving a clear diagnosis of PCOS [7,8,10]. Serum AMH levels in PCOS women correlate with other clinical features like mean ovarian volume, testosterone levels, free androgen, cycle duration [7].

Purpose of study

Saunhagya Kumar Jena, et al. (2020) conducted a study to find the perception and awareness of PCOS and its prevalence among young women [11]. The period taken for the study was about 2 years, a validated questionnaire was formed, descriptive analysis was used. Most aware women were from urban areas [11]. The study conclusion suggests awareness and knowledge about PCOS in women in rural areas were very low and need to be improved [11]. As PCOS is a very common condition nowadays, there is a need for awareness regarding PCOS among reproductive women. according to the present scenario, a major risk factor for the occurrence of PCOS is the lifestyle of women. Nowadays most women in the urban areas are consuming junk foods and high fatty foods, with less or no physical activity, which increases obesity and hence the risk. The benefit of conducting this study is that we get a closer outlook on the health issues regarding PCOS, as it is an emerging health concern among young girls. It will provide access to information about clinical features and biological problems related to a patient directly. PCOS is considered a syndrome, due to its diversity of clinical presentation in various patients. The various manifestation that is presented is irregular cycles of menstruation, scanty flow, hirsutism, acne, hair-fall, acanthosis nigricans, etc. These symptoms are also accompanied by metabolic irregularities like diabetes mellitus, or thyroid issues, hypertension, and infertility. This study will help to differentiate between these complications and will help to find out the association of them with the occurrence and severity of PCOS. Until now, only the Rotterdam criteria are being used to diagnose the PCOS condition. As per the review of literature conducted, we found that Anti- Mullerian hormone levels also have a close association with PCOS. The AMH level shows signs of anovulation, which leads to polycystic ovarian disease. AMH levels also correlate with the severity of PCOS. So, in this study, we are aiming at finding a correlation of AMH levels in PCOS, thereby establishing AMH levels as a biomarker of PCOS and possibly a new diagnostic tool in PCOS.

Objective

- To assess the incidence of PCOS patients coming to the Gynecology-Obstetrics OPD
- To evaluate the clinical presentation of PCOS
- To assess the role of Anti-Mullerian hormone levels among PCOS patients
- To assess the role of genetic predisposition in PCOS

Ethical approval

The study was duly approved by the Institution Ethics Committee ahead of the start of the work.

METHODOLOGY

Study Design

It is a prospective observational study.

Study Site

Department of Gynecology and Obstetrics OPD at SMI Hospital, Dehradun.

Study Duration

Approx. 8 months

Sampling methods

Inclusion criteria:

- Females of reproductive age having symptoms of PCOS
- Females who have relevant biochemical data values suggestive of PCOS
- Females who have ultrasound suggestive of Polycystic ovaries
- Females who have elevated Anti-Mullerian Hormone levels

Exclusion criteria:

- Pre-adolescent females
- Post-menopausal females
- Psychiatric patients who have PCOS
- Pregnant females

A prospective observational study was carried out in the Gynecology & Obstetrics OPD at SMI Hospital, Dehradun. A self-designed questionnaire-based study was conducted on subjects with symptoms of Polycystic Ovarian Syndrome. The study proposal was approved by the Institutional Ethics Committee. The consent of the subject was taken according to the Informed Consent Form prior to the data collection. The eligibility criteria were: Females of reproductive age having symptoms of PCOS, Females who have relevant biochemical data values suggestive of PCOS, Females who have ultrasound suggestive of polycystic ovaries, Females who have elevated Anti-Mullerian hormone levels. Rotterdam criteria were used for the diagnosis of PCOS. The following details were obtained from the subjects: Demographic details(name, age, marital status, address), Family history (Diabetes mellitus, thyroid, Hypertension, mother's and sister's menstrual history, PCOS history, infertility, and other relevant details), Social history, Gynecological history(age of menarche, duration of the menstrual cycle, length of menses, and flow in the menses) Clinical features(acne, hirsutism, hair fall, mood swings), and Personal habits(tea-drinking habits, alcohol intake, junk-food intake, and physical activity).

Weight and height were measured by standard protocol and calibrated instruments to calculate the BMI. Calibrated sphygmomanometer was used to measure the blood pressure to assess hypertension. Hirsutism was assessed bases on the hair growth in upper lips, chest, chin, upper and lower abdomen, thighs, upper and lower back, and upper arms. This is referred to as the Ferriman-Gallwey method. The severity of acne was assessed by the Global acne scoring method. Blood test reports of biochemical estimation of hormones like LH, FSH, and serum AMH were collected. Ultrasonography reports indicating PCOS morphology were collected. After the data collection, the data was entered into Microsoft Excel and further calculations were done. All the mean values and standard deviations were calculated by appropriate methods in Excel. For the calculation of correlation between the risk factors and serum AMH levels, Chi-square test was used in SPSS 25 software and results were calculated accordingly [13-20].

RESULTS

A total number of 2500 women were screened and evaluated for PCOS during the study period. According to the study conducted, the incidence of PCOS among patients attending the Gyne-Obs OPD was calculated. Out of 2500 women, 600 was found to have PCOS, as diagnosed by the Rotterdam criteria. By this, we concluded that the incidence rate of PCOS was 0.24 cases per person-time at risk, the age group with the highest number of PCOS patients was 21-25 years and the mean age of women diagnosed with PCOS was 24± 4.96 years. The risk- factors taken into consideration were **(Tab. 1- 5)**:

Duration of the period cycle

- Junk-food habits
- Flow in menses
- Physical exercise
- History of diabetes mellitus
- Body mass index (BMI)
- History of hypertension
- History of the thyroid
- Family history of diabetes mellitus
- Family history of hypertension
- Family history of thyroid issues
- Gynecological history in mother/sisters
- Tea-drinking habits

As per the significance value calculated by the Chi-square test, the duration of the period cycle has a direct effect on the serum AMH levels, and therefore, on the occurrence of PCOS. The $p<0.05$ and the correlation coefficient was 1.404. This shows that the irregular menstrual cycle accounts for the occurrence of PCOS. The cycles are considered to be irregular if the number of days is 30 ± 7 days. Most women who had elevated AMH

Tab. 1. Distribution of patients according to age.

Age Group (years)	Number of Patients	Percentage (%)
15-20	102	17%
21-25	294	49%
26-30	138	23%
31-35	48	8%
36-40	6	1%
41 and above	12	2%

Tab. 2. Distribution of patients according to BMI.

BMI (kg/m²)	Category	Number	Percentage (%)
<18.0	Underweight	36	6%
18.1-24.9	Ideal	222	37%
25.0-29.9	Overweight	222	37%
30.0-34.9	Obese class I	96	16%
35.0-39.9	Obese class II	24	4%
>40.0	Obese class III	-	-

Tab. 3. Complications of PCOS.

Conditions/Complications	Number	Percentage (%)
Oily skin	498	83%
Acne	420	70%
Hirsutism	360	60%
Alopecia	294	49%
Acanthosis nigricans	126	21%

Tab. 4. Range of AMH levels in PCOS women.

Range of AMH levels (ng/ml)	Percentage of women (%)
<3	5%
3.0-6.0	31%
6.1-9.0	37%
9.1-12.0	18%
12.1-15.0	6%
>15	3%

Tab. 5. Chi-square analysis.

Risk-factor	p-value	Coefficient	Remarks
Duration of period cycle	p<0.001	1.404	Significant
Flow in menses	p<0.001	1.608	Significant
History of Diabetes Mellitus	p<0.001	1.005	Significant
History of Hypertension	p<0.001	1.004	Significant
History of thyroid	p<0.001	1.03	Significant
Family history of diabetes mellitus	p<0.001	1.013	Significant
Family history of hypertension.	p<0.001	1.079	Significant
Family history of thyroid issues	p<0.001	1.034	Significant
Gynecological history in mother/sisters	p<0.001	1.393	Significant
Caffeinated drinks	0.304	0.52	Non-significant
Junk-food habits	0.763	0.593	Non-significant
Physical exercise	0.293	0.682	Non-significant
Body Mass Index (BMI)	p<0.001	1.132	Significant

levels also had a history of irregular cycles. Similarly, the menstrual flow was also significant to AMH changes in PCOS women **(Fig. 1-8)**. The p-value was p<0.05 and the correlation coefficient was 1.608. Most women with PCOS had scanty flow during their menses. Some even had spotting. History of disorders like hypertension, diabetes mellitus, and thyroid are also significant to PCOS. It was found that women, who had these conditions, were at a higher risk of development of PCOS, as they all had a significant correlation with serum AMH levels. The percentage of women who had diabetes mellitus was 4%, 3% of women were hypertensive and 24% of women had thyroid issues.

DISCUSSION

Beyond The association between obesity and COVID-19 can be assessed in various aspects. First obesity causes respiratory system dysfunctions like decreased chest wall elasticity (fat in the abdomen pushes up on the diaphragm, which presses on the lungs and restrict airflow) lung compliance, and expiratory reserve volume (this reduced lung volume causes collapse of airways in the lower lobes of the lungs, where more blood arrives for oxygenation than in the upper lobes) [7]. Second, obesity is associated with disorders such as type 2 diabetes mellitus, atherosclerosis, cardiovascular diseases, hypertension and cancer [8].

Fig. 1. Distribution of patients according to age.

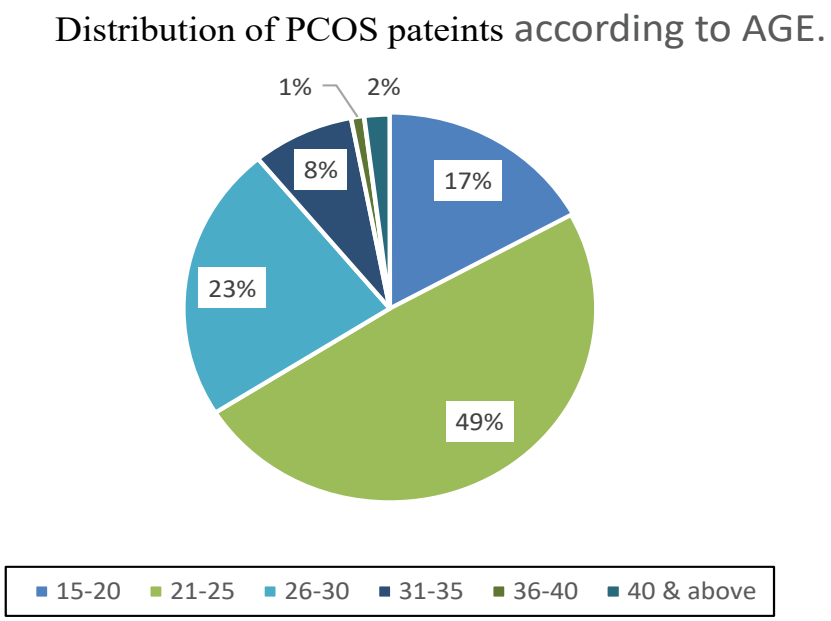


Fig. 2. Distribution of patients according to BMI.

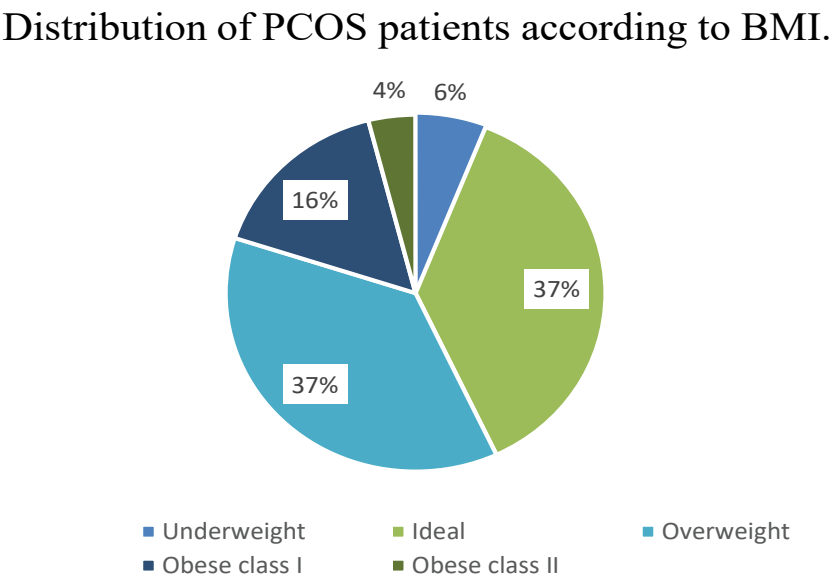
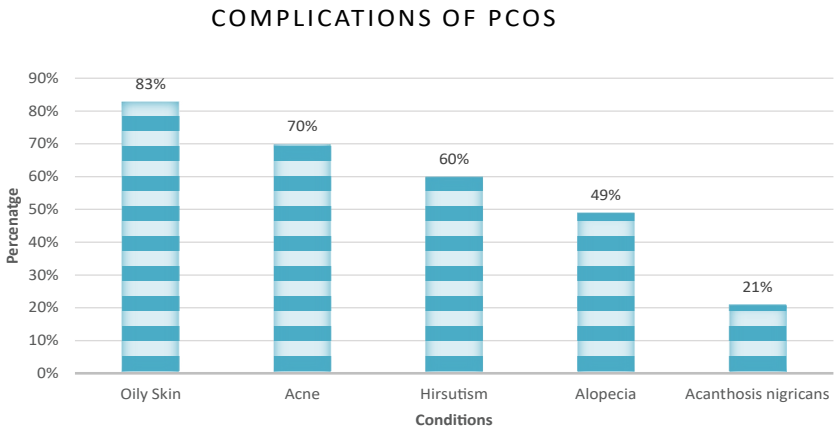


Fig. 3. Complications of PCOS.



Which are also identified as risk factors for COVID-19. These comorbidities may exacerbate COVID-19 and increase the probability of hospitalization in the intensive care unit (ICU) and also increase mortality [9]. Third, it leads to hyper coagulopathy state and hyper inflammation, and it is well known that venous thromboembolism is a complication of severe COVID-19 infection as well, thus these 2 conditions when present together produce

Fig. 4. Occurrence of acne.

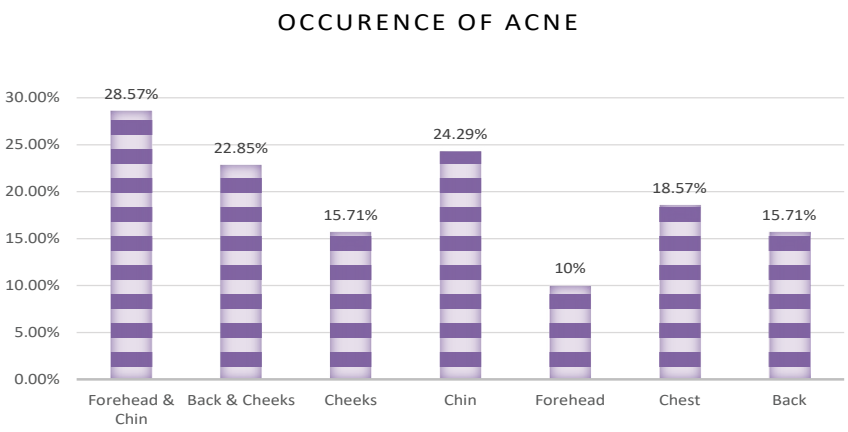


Fig. 5. Presence of hirsutism. The occurrence of Hair-fall was also evaluated in the subjects and it was found that 49% of women had hair fall issues while 51% did not.

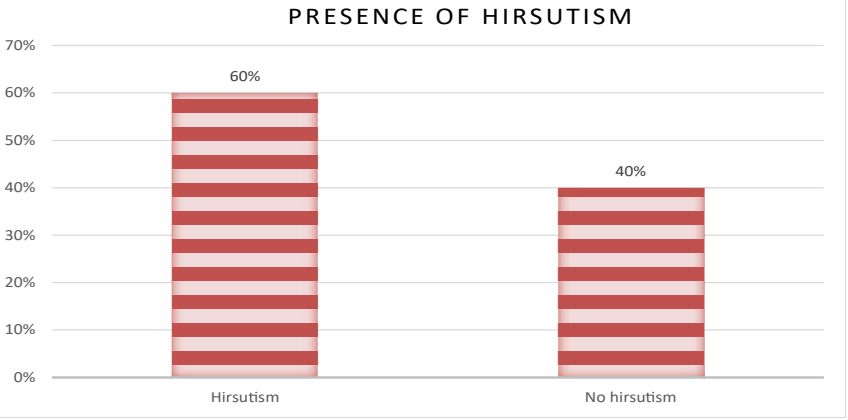


Fig. 6. Presence of hirsutism.

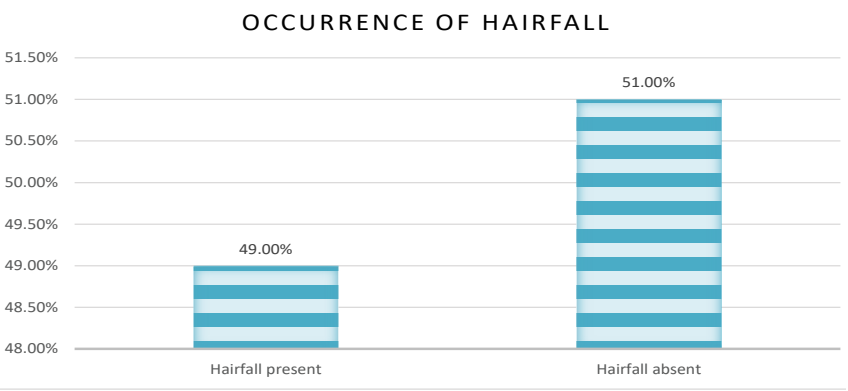
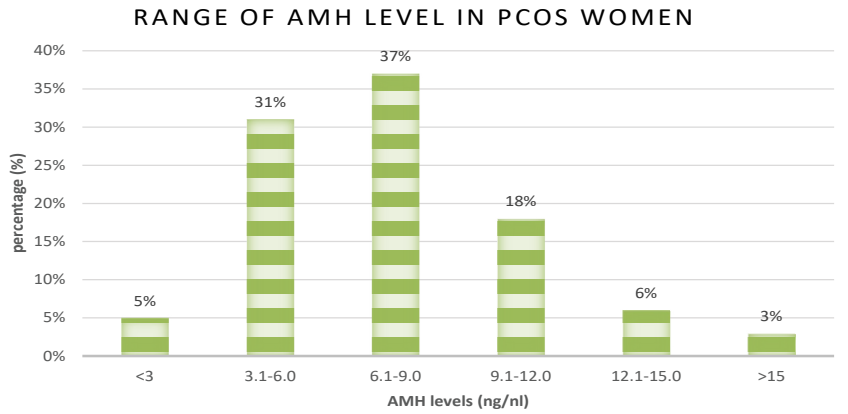
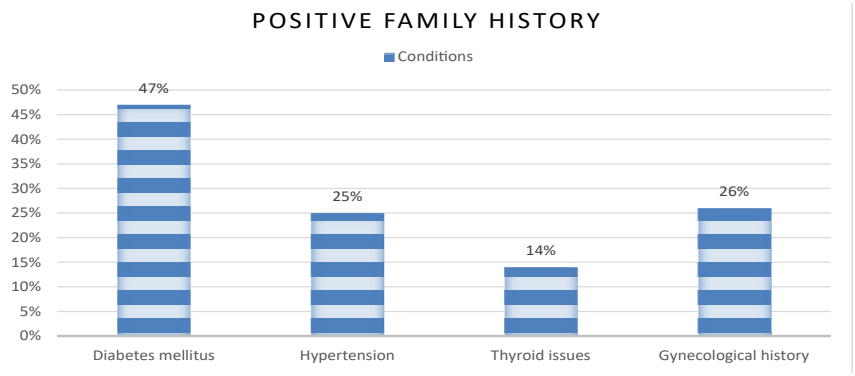


Fig. 7. Range of AMH levels in PCOS women.



hypercoagulability and thromboembolism in a synergistic way. Inflammatory markers such as IL-6 and C-reactive protein are increased in obese patients [10,11]. These may become so severe that they can cause clots in vital organs and cytokine storm. In all these 3 conditions, the disease is severe and the risk of admission to the ICU and mortality is high. On the other hand, COVID-19 also has an impact on obesity as it increases social constraints and impedes

Fig. 8. Positive family history.



mobility, which thus increases the weight and prevalence of obesity in society, and this gives way to a vicious cycle that is repeated all over again and again. Although there are ample advantages of bariatric surgery in the COVID-19 patient, there are certain limitations that are worthy of mention. Bariatric surgery, specifically bypass surgery, is likely to have an effect on the absorption of medications that are administered orally to COVID-19 patients. In case of hydroxychloroquine, a case report of three post-RYGB (Roux-en-Y procedure) patients with autoimmune disease was done (taking standard hydroxychloroquine doses), all three patients had sub therapeutic hydroxychloroquine blood levels and active disease; it was only after increasing their doses above the recommended 400 mg/day dosing that they were able to have therapeutic drug levels as well as better disease control. Thus hydroxychloroquine has inadequate absorption post-RYGB (and potentially other bariatric procedures), and COVID-19 bariatric patients may need higher doses of hydroxychloroquine than recommended [12]. For azithromycin a single-dose pharmacokinetic study involving 14 post-gastric bypass patients showed that bioavailability was reduced by 1/3rd in gastric bypass patients, when compared with matched controls [13]. Since maximal absorption of azithromycin occurs in proximal gut. During RYGB (Roux-en-Y procedure) the stomach is dissected, that leads to less acidic gastric pouch. Azithromycin with its basic nature (alkaline; pKa=8.5) and low water solubility, the dissolution of the large (500 mg) drug dose of azithromycin can be severely affected post-surgery thus affecting the absorption and bioavailability of azithromycin. In case of corticosteroids, the pharmacokinetics of dexamethasone and related steroids may be affected especially post-gastric bypass surgery. These drugs are mainly absorbed via the proximal gut which is hampered during the bariatric procedure. These are some of the limitations of the bariatric surgery procedure that need to be considered in a COVID-19 patient.

CONCLUSION

In In conclusion, the present study suggests that PCOS is an emerging health concern among reproductive women and is associated with many consequences like menstrual irregularities, hirsutism, acne, alopecia, and infertility, which were common endocrine disorders. Family history of diabetes and hypothyroidism were important risk factors associated with PCOS. Women who were overweight/obese were at a higher risk of developing PCOS. History of menstrual irregularities and PCOD/PCOS in mother and sisters of women also had significance in the occurrence of PCOS. Special attention should be paid to overweight and obese girls as they were having the highest possibility of PCOS but it could be treated by lifestyle modification. Thus, early detection of the syndrome based on clinical findings (mainly oligo- or amenorrhea) offers an opportunity for early intervention to prevent or limit the impact of cutaneous and reproductive symptoms, and the long-term effects of metabolic disturbances. Further, the emerging role of Anti-Mullerian Hormone should be recognized in the diagnosis of PCOS along with other suggestive features. AMH levels are the most reliable measure of follicle count in the ovaries. In PCOS, the ovaries fail to select a dominant follicle to ovulate and a number of small follicles are developed, which are filled with fluid and are called cysts. These cysts produce AMH and so the levels of AMH increases in PCOS. AMH levels will provide reliable information in diagnosing PCOS and should be used in future along with Rotterdam or NIH criteria. Awareness of earlier diagnosis of PCOS and interventions must be increased among health care providers and adolescent girls because it could provide an opportunity to treat this disease and prevent future morbidities.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY

All data generated or analyzed during study are included in this review.

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