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RESEARCH ARTICLE

ROLE OF ANTI-MÜLLERIAN HORMONE (AMH) IN ASSESSMENT OF THE POLYCYSTIC OVARY SYNDROME (PCOS) SEVERITY; A REVIEW

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Abstract

Introduction: The hormone anti-Müllerian hormone (AMH) is produced by granulosa cells in the ovary and has emerged as a potential biomarker for PCOS. The AMH value increases in proportion to the severity of PCOS; thus, serum levels of AMH may be a marker for polycystic ovary syndrome and have a diagnostic role in determining the severity of PCOS.

Aim: to determine PCOS severity based on the current available literature of the role of AMH.

Methods: PubMed, Medline, Embase, and the Cochrane Library were used to conduct this systematic review. Key terms related to POS severity, as well as AMH as an indicator of POS severity, were used to find related studies published between January 2018 and January 2023. Abstracts from all related articles addressing the role of AMH in POS severity assessment were included and reviewed.

Results: Ten articles were included, and serum AMH levels were significantly higher in PCOS cases than in controls in the seven included case-control studies. Other studies discovered that AMH levels were strongly related to both sonographic markers studied and mean ovarian volume. Other studies discovered a significant increase in serum AMH levels in PCOS patients, as well as a statistically significant decrease in AMH levels after PCOS treatment.

Conclusion: There is evidence that AMH contributes to the severity of PCOS and plays a critical role in PCOS pathophysiology. More experimental research is needed to better understand the AMH-related pathophysiology of PCOS, which could lead to the development of new treatments for this condition.

Introduction:-

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age with a prevalence of 9-18% (March, 2010). According to the Rotterdam criteria used to diagnose PCOS, it requires the presence of two out of three of the following symptoms: polycystic ovarian morphology

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(PCOM) on ultrasound, clinical or biochemical hyperandrogenism (HA), and oligo/amenorrhea (OA) or ovulatory dysfunction (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2003;Bustin et al., 2009). Despite its high prevalence with 9-18%, the pathophysiology of PCOS is not fully understood Nonetheless, PCOS diagnosis can be difficult because counting ovarian follicles and measuring ovarian volume with ovarian ultrasound are operator-dependent (Sahmay et al., 2013).

Anti-Müllerian hormone (AMH), a glycoprotein hormone produced by granulosa cells in the ovary, has emerged as a potential biomarker for PCOS due to its role in folliculogenesis and its correlation with the number of small antral follicles. Recent research on various aspects of PCOS has provided new insights into the disease's assessment and treatment. The link between PCOS and anti-Müllerian hormone (AMH) is gaining attention because AMH is important in ovarian function. It preserves the primordial follicles and estimates the number of ova in the ovaries, providing an indication of the ovarian reserve (Durlinger et al., 2002; Grynnerup et al., 2012)).

The objectives of this study are to determine the levels of AMH in women with PCOS and compare them to those without PCOS, investigate the correlation between AMH levels and the severity of PCOS symptoms, assess the relationship between AMH levels and the number and size of ovarian cysts in women with PCOS, and explore the potential of AMH as a diagnostic tool for PCOS.

Furthermore, the study aims to evaluate the usefulness of AMH as a prognostic marker for PCOS by assessing its ability to predict the response to treatment and the risk of long-term complications such as infertility and metabolic disorders. The study will also identify any potential confounding factors that may affect AMH levels in women with PCOS, such as age, BMI, and ethnicity, and investigate the impact of lifestyle interventions, such as diet and exercise, on AMH levels and PCOS symptoms. Also, the study aims to investigate the potential of AMH as a biomarker for the evaluation and severity of PCOS in women of reproductive age.

Overall, this study has the potential to provide a more accurate and reliable assessment of PCOS severity using AMH levels, which may help in the early diagnosis and treatment of PCOS and improve the long-term reproductive and metabolic health outcomes for women with this condition.

AMH and PCOS:

AMH is produced by granulosa cells in the ovary and is involved in the regulation of folliculogenesis. It inhibits the recruitment of primordial follicles and the growth of small antral follicles, thus maintaining the pool of growing follicles in the ovary. In women with PCOS, AMH levels are elevated due to an increase in the number of small antral follicles. This increase in AMH is seen in both lean and obese women with PCOS and is independent of body mass index (BMI). Furthermore, studies showed that serum AMH levels are related to the number of antral follicles, which is increased in PCOS and polycystic ovarian morphology (PCOM) (Lavenet al., 2004; Pigny et al., 2006).

Patients with PCOS had higher serum AMH levels due to a greater number of antral follicles and higher AMH production per follicle (Bhideet al., 2015;Nardoet al., 2009). This could imply that AMH plays a significant role in PCOS diagnosis (Dewailly et al., 2011). AMH levels greater than 5 ng/mL have been proposed to replace the current method of diagnosing PCOM, while 3.8 ng/mL and higher have been recommended by another study (Sahmayet al., 2014).

AMH as a diagnostic tool and PCOS severity:

The Rotterdam criteria, which are commonly used to diagnose PCOS, require the presence of two out of three criteria: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries on ultrasound (Pioukaet al., 2009). However, the presence of polycystic ovaries on ultrasound is not specific to PCOS and can be seen in other conditions such as hypothalamic amenorrhea and premature ovarian failure(Wiwekoet al., 2014). AMH has been suggested as a more specific biomarker for PCOS due to its correlation with the number of small antral follicles, which is a hallmark of PCOS. Several studies have shown that AMH levels are significantly higher in women with PCOS compared to women without PCOS, and that AMH can be used to diagnose PCOS in the absence of polycystic ovaries on ultrasound ((Wiweko et al., 2014).The AMH value increases in proportion to the increase in the severity of PCOS, therefore, it is suggested that serum levels of AMH may be a marker for polycystic ovary syndrome. AMH levels seem to have a diagnostic role in determining the severity of PCOS (Soyman, 2021). AMH levels have been shown to correlate with the severity of PCOS. Women with more severe PCOS, as defined by the presence of both hyperandrogenism and ovulatory dysfunction, have higher AMH levels compared to women with

less severe PCOS. AMH has also been shown to correlate with other markers of PCOS severity such as insulin resistance, BMI, and hirsutism(Pioukaet al., 2009; Wiwekoet al.,2014; Soyman, 2021).

AMH and response to treatment:
AMH has been suggested as a potential predictor of response to treatment in women with PCOS. Several studies have shown that women with higher baseline AMH levels have a poorer response to ovulation induction with clomiphene citrate and gonadotropins, and that AMH levels can be used to predict the number of oocytes retrieved during in vitro fertilization (IVF) treatment. However, the use of AMH as a predictor of treatment response in PCOS is still controversial, and further studies are needed to validate its use in clinical practice (Vagios et al., 2021).

Search Strategy
The present systematic review was carried out using PubMed, Medline, Embase and Cochrane Library. Key terms related to assessment of severity of POS, AMH as an indicator of POS severity were used to search for related studies that were published from January 2018 to January 2023. Abstracts of all related articles addressing the role of AMH in the assessment of POS severity were reviewed. The reference lists of included articles and recent reviews which dealt with the same subject were examined.

Inclusion criteria
All relevant articles published in English from January 2018 to January 2023 that addressed the role of AMH in the assessment of POS severity were included after consultation with an Oby/Gyne expert.

Exclusion criteria
All reviews, duplicate publications, and studies that did not include AMH measurements were excluded.

Data Extraction
One investigator extracted data on the following topics: authors, year of the study, sample size, study design, sample size, AMH analysis, result, and conclusion. Another investigator independently reviewed the extracted data's accuracy.

Assessment of study risk of bias
Two investigators independently assessed the methodological quality of selected studies. To assess the risk of bias, pre-specified questions for each study design were used, and studies with a high risk of bias were excluded (Viswanathan et al., 2008).

Results:-

The current review included ten articles that included 3856 women. One was a cross-sectionalstudy(Wafa et al., 2018), seven studies had a case-control study design (Nardoet al., 2009; Soyman, 2021;Ozayet al., 2020; Ahmed et al., 2019; Singh et al., 2020; Ran et al., 2021; Rana et al., 2021, and three were prospective studies (Singh et al., 2020; Rana et al., 2021; Meena et al., 2021) including a prospective cases control study (Singh et al., 2020). Reviewed studies and their publication year, study design, sample size and timing of analysis were shown in table 1.

The included articles that assessed the possible role of AMH as the diagnostic marker for different degrees of PCOS. Other articles examined the association of serum AMH levels with biochemical derangement and sonographic appearance in PCOS patients. And others determined whether the measurement of serum AMH can be used to diagnose PCOS and as a tool to predict the prognosis of PCOS.

In the seven included cases -control studies, serum level of AMH was significantly higher in the cases than in controls (Soyman, 2021; Sharma et al., 2019;Ahmed et al., 2019;Ozayet al., 2020; Singh et al., 2020; Ran et al., 2021; Rana et al., 2021). In the cross-sectional study done by Wafa et al., AMH levels correlated strongly with both sonographic markers studied and mean ovarian volume (Wafa et al., 2018). As for the prospective observational studies included in the review (24,25), Rana and Randhawa (Rana et al., 2021) divided the participants into 4 groups:

1. group 1 (PCOM+OA+HA),
2. group 2 (PCOM+OA),
3. group 3(OA+HA), and
4. group 4 (OA+PCOM).

They found that the highest levels of AMH were found in Group 1 (PCOM+OA+HA) compared to other groups. Meena et al., (Meena et al., 2021) found a marked increase in serum AMH levels in PCOS patients and there was statistically significant decrease in AMH level following treatment of PCOS.

Discussion:-

The current review included studies with the same goal in mind: to investigate the role of AMH in determining the severity of PCOS. Seven of the included studies used a control group to account for potential variability (Soyman, 2021; Sharma et al., 2019; Ahmed et al., 2019; Ozay et al., 2020; Singh et al., 2020; Ran et al., 2021; Pandey et al., 2023).

The serum level of AMH was discovered to be a diagnostic marker for PCOS in the Wafa et al (2018) study (Wafa et al., 2018). They found that the serum level of AMH could be used as a diagnostic marker for PCOS. They compared AMH levels in three groups based on PCOS severity: severe PCOS, mild PCOS, and controls. The serum level of AMH was significantly higher in women with PCOS compared to the control group. Serum AMH levels were highest in group 3 (severe PCOS) and lowest in group 1. (control). Women with severe PCOS had higher serum AMH levels than regular cycling women (control), regardless of mild PCOS, and women with PCOM (mild PCOS) had higher serum AMH levels than women without PCOM (control), regardless of PCOS. The study concluded that AMH could be used as a reliable diagnostic marker for PCOS, with a sensitivity of 96.7% and specificity of 90%. These findings suggest that AMH could be a useful tool for the early diagnosis and treatment of PCOS, which could improve the long-term health outcomes for women with this condition.

The evaluation of serum AMH levels has been shown to be a reliable diagnostic marker for PCOS. Previous study showed that the evaluated serum AMH levels in the diagnosis of PCOS and found a satisfactory specificity of 92% but a low sensitivity of 67% with an AMH cut-off of 8.4 ng/mL (60 mol/L) and a mean serum AMH of 11.42 ng/mL (81.6 mol/L) (Pignyet al.,2006). The levels of AMH are typically higher in women with PCOS compared to those without the condition, which can aid in the early diagnosis and treatment of PCOS. This diagnostic approach has been found to have high sensitivity and specificity, making it a useful tool in the clinical setting. By using serum AMH levels as a diagnostic marker for PCOS, healthcare providers can improve patient outcomes by providing early intervention and management of this common endocrine disorder. This study was supported by other studies found that serum AMH levels were elevated in adolescent with PCOS (Sharmaet al., 2019; Li et al., 2011), and finding consistent with the findings of other studies (Sahmay et al., 2014; Saxena et al., 2018). AMH was discovered to be a suitable hormonal marker of ovarian follicular count, and serum AMH levels are thought to be an indirect reflection of ovarian reserve. AMH levels have been found to be higher in more severe disease phenotypes (Köninger et al., 2014), and to correlate well with the individual Rotterdam criteria (Köningeret al., 2014;Hayes et al., 2016).

Because AMH is produced by pre-antral and small antral follicles, its levels are expected to rise in PCOS, which has an abundance of such follicles. AMH most likely inhibits the FSH-mediated folliculogenesis process, resulting in anovulation. In PCOS, a higher AMH/AFC (antral follicle count) ratio indicates not only a greater number of antral follicles, but also increased AMH production per antral follicle (Bhide et al., 2015). This observation is supported by in vitro studies, which show that polycystic ovaries produce more AMH per granulosa cell than controls (Pellatt et al., 2007).

There is a strong positive correlation between AMH serum levels and mean ovarian volume and antral follicle count in PCOS women and mean ovarian volume alone in controls(Sharma et al., 2019; Ahmed et al., 2019).AMH levels were found to be a good substitute for PCO morphology in the diagnosis of PCOS using both the AMH and Rotterdam criteria (Eilertsen et al., 2012). Other studies found a link between AMH levels and ovarian volume and antral follicle count. As a result, AMH has been proposed as a substitute for sonographic findings, particularly in cases where imaging is unavailable or likely to be suboptimal, such as obesity and virginal status (Pigny et al., 2006; Dewailly, 2016). It wasfoundthat a two-fold increase in AMH over controls, and women with PCOS who had AMH levels greater than 3.19 ng/mL had a higher prevalence of PCOM and OA (Saxena et al., 2018; Sathyapalan et al., 2018).

A confirmed finding of high serum AMH levels in PCOS women when comparing them to healthy women and women with polycystic ovarian morphology only and were two to three times higher than in women without PCOS. Furthermore, AMH levels in PCOM patients were statistically lower than in all other PCOS phenotypes. The highest

AMH levels were also found in phenotype A, which exhibited all three symptoms of the syndrome. PCOS phenotype A, AMH levels were statistically significantly higher than PCOS phenotype D (21,22). It was suggested that AMH is a good tool for assessing the antral follicle pool because serum AMH concentrations have a strong relationship with the antral follicle count,concluded that AMH levels can be used to replace follicle count as a diagnostic criterion (Ozay e al., 2020;Bhide&Homburg, 2016).

It is found that women with PCOS had significantly higher AMH levels than controls, even if they did not have hyperandrogenism (HA) or polycystic ovary morphology (PCOM), which also found that AMH was related to the severity of the PCOS phenotype (Ran et al., 2021). The level of AMH in the PCOM subgroup was significantly higher than in the HA subgroup. It was discovered that increased AMH suppresses aromatase expression in granulosa cells and prevents androgen conversion to estrogen, which contributes to the increased androgen level, this mutually reinforced interaction between AMH and HA could explain PCOS(Jacob et al., 2017).AMH levels were higher in POM phenotypes than in women without PCOS,these findings support the theory that POM causes increased AMH levels. Increased AMH levels may also aid in the diagnosis of PCOS in the oligo-ovulation or anovulation (OA) +POM group, which has a normoandrogenic profile. Thus, it is concluded that increased AMH levels may play a role in detecting the severity of PCOS (Soyman, 2021).

Prospective studiesshowed thatserum AMH levels increased significantly in PCOS patients (Meena et al., 2021). AMH production was found to be approximately 75 times higher in each polycystic ovarian granulosa cell (Pellatt et al., 2010). AMH levels were compared among four major PCOS phenotypes that were classified using three widely accepted criteria: PCOM, OA, and HA.The study found high circulating AMH levels in the group that met all three criteria. These findings suggest that PCOM is the most effective factor in influencing AMH levels. AMH serum levels were found to be highly correlated with parameters such as oligo/anovulatory periods, which indicate the severity of ovarian dysfunction (Ahmed et al., 2019).According to other studies there is a significant relationship between serum AMH levels and increased testosterone, LH levels and increased follicle number and ovarian volume on ultrasound examination (Lavenet al., 2004; Pandey et al., 2023; Wang et al., 2007). These studies concluded that AMH not only reflects antral follicle count (AFC), but also the degree of hyperandrogenism, making AMH a better marker than follicle numbers per ovary.

Table 1:- Reviewed studies and their publication year, study design, sample size and timing of analysis.

Authors	Year	Study design	Sample size	women age
Wafa et al. [17]	2018	cross-sectional study	150 (50 POS sever cases, 50 mild cases and 50 controls)	18-40 years
Sharma et al [18]	2019	case-control study	90 (45 POS cases and 45 controls)	18-45
Ahmed et al [19]	2019	case-control study	148 (79 PCOS cases and 69 controls)	23 ± 9 and 21 ± 3.5 for cases and controls
Ozay et al. [20]	2020	case-control study	350 (71 POS cases and 79 controls)	24.86 ± 4.17 and 24.05 ± 4.59 for cases and controls
Singh et al. [21]	2020	prospective case control study	100 (50 POS cases and 50 controls)	18-39 years
Ran et al. [22]	2021	case-control study	2262 (1631 POS cases and 631 controls)	16-29
Soyman [15]	2021	case-control study	146 (116 POS cases and 30 controls)	22-25
Rana and Randhawa [23]	2021	Prospective study	200 POS cases	14-35 years
Meena et al. [24]	2021	prospective study	70 POS cases	mean age was 21.54 years
Pandey et al. [25]	2023	case-control study	340 (170 POS cases and 170 controls)	18-40 years

Conclusion:-

This review summarizes the existing evidence regarding AMH's contribution to the severity of PCOS and its critical role in PCOS pathophysiology. As a result, studying AMH can help us learn more about ovarian physiology and pathophysiology. More basic and experimental research will be critical in better understanding the AMH-related pathophysiology of PCOS, which may lead to the development of new therapies for this disorder. Furthermore, future evaluation of AMH's role in the diagnosis of the various subcategories of PCOS that will inevitably exist with the current classification system is required.AMH has emerged as a potential biomarker for PCOS due to its correlation with the number of small antral follicles, which is a hallmark of PCOS. AMH levels have been shown to be elevated in women with PCOS and to correlate with the severity of the disorder. AMH may also be useful in predicting response to treatment in women with PCOS. Overall, AMH has the potential to improve the diagnosis and management of PCOS.

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Conflicts of interest:
No conflicts related to this work

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