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SM Journal of Endocrinology and Metabolism

Review Article

Polycystic Ovary Syndrome: An Epidemic in Women's Health and Why it Matters

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Article Information

Received date: Mar 14, 2017
Accepted date: Apr 12, 2017
Published date: Apr 17, 2017

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Keywords Polycystic ovary syndrome; PCOS; Polycystic; Ovarian; Rotterdam criteria; Serum-AMH; Women's health; Reproductive health

Abstract

Polycystic ovary (ovarian) syndrome, or PCOS is predominantly a reproductive health issue affecting women of reproductive age, though argued it can be defined as young as age 13 and through to early pre-menopausal age cohorts. Currently, the Rotterdam criteria are used in PCOS diagnosis: However, new research and understanding suggest that this method is since outdated from its original 2003 definition. However, no systematic research has been conducted that fully generalizes women globally affected by PCOS. The use of serum-AMH in diagnosis of PCOS reveals a higher sensitivity (92) and specificity (97) level than those of the Rotterdam criteria; 81 and 92 percent respectively. The contrast between these two opposing methods of diagnosis creates a large gap in PCOS prevalence worldwide, with serum-AMH suggesting nearly 23 percent of women globally being affected by PCOS, opposed to the 16 percent based upon current methods. The purpose of this proposal is to provide just because for redefining diagnostic techniques, in association with PCOS globally, using serum-AMH levels as PCOS markers versus morphology. By conducting an initial online survey with the option to participate in serum level and follicle counting tests, a more global view of PCOS and PCOS diagnosis methods/tools can potentially be seen. Furthermore, a call to change how PCOS is approached on a diagnostic level could potentially be found in accordance with a wider spanning study population.

Proposal Background

Polycystic ovary syndrome, or PCOS, is an endocrine, pancreatic and reproductive health issue affecting between 6 and 23 percent [1,2] of women of reproductive age [3]. The syndrome is commonly characterized by hyperandrogenism (increased androgen levels), hyperinsulinemia (increased insulin levels and/or sensitivity), obesity, infertility, hirsutism (presence of excess body hair) and oligo-ovulation (irregular menses) [3].

PCOS is a syndrome that has a complicated set of phenotypic characteristics, in which there is no one "gold standard" for diagnosis [4]: PCOS thus brings many challenges to the health and medical fields – because it is a syndrome that has multiple definitions depending on the authors' perspectives and its many possible phenotypic manifestations-it becomes hard to pinpoint exactly what PCOS is and how it is caused. Furthermore, past research has suggested higher prevalence among certain population groups over others, due to ethnic differences [4], however the validity of this is not fully adapted or understood.

Previous descriptions and criteria for diagnosis are hardly perfect, and are constantly being challenged. The Rotterdam criteria for instance, does not account for the flexibility needed to include more moderate forms of PCOS, and becomes a game of exclusion over inclusion (based on other properties) [4]. Furthermore, to this point, definition/characteristic differences, in addition to different hypotheses on causes, and treatment options, have created an unsure method of diagnosis and prognosis.

Proving even more taxing is the diagnosis of PCOS in adolescents. During the adolescence stage of life, proving PCOS via an ovulatory symptoms is not enough, clinical and/or biochemical evidence is needed to prove hyperandrogenism, once all other pathologies have been excluded [2,5]. The below method could prove a more systemic method of PCOS diagnosis among adolescents.

With diagnosis prevalence increasing as more is being learned about PCOS, there is still an air of misunderstanding, and potentially misdiagnosis, among women globally. Further research into proposed methods of systematic diagnosis could potentially change the way PCOS is approached. Dewailly et al. [1] proposed using the high serum levels of Anti-Müllerian Hormone (AMH), (a peptide produced from the Granulosa Cells (GC) of ovarian follicles), over counting ovarian follicle numbers, to, not only simplify, but produce an easier case-to-case method of PCOS diagnosis: Previously Polycystic Ovarian Morphology (PCOM) via follicle counting and measuring during ultrasounds, were seen as the only solid method of determining PCOS via "cysts."

Serum-AMH functions as an inhibitor to the production and adulteration of viable ovum. Due to serum-AMH being an androgen that, during fetal development can opt to produce portions of the ovaries, uterus and fallopian tubes, or produce testes, in women with PCOS, serum-AMH remains high post-fetal development [6]. The high incidences of serum-AMH result in antral follicles under-producing and therefore not reach maturation, causing ovum to not be released during menses. The eventual buildup of antral follicles, and androgens in the system, can lead to the umpteenth side-effects associated with PCOS [6].

While there are proposed methods of systematic diagnosis, it has yet to become fully accepted and adopted as a process, even though studies have shown its significance [1]. Since a divide appears in the methodological approach to PCOS, more research (and conversation) needs to occur in order to solidify practices of diagnosis and prognosis. By understanding more about current practices, their differences, and their consistency in the overall process, a better understanding and implementation of newer practices could potentially change how PCOS is approached.

Literature Review

PCOS is becoming an epidemic in women's health, however, little is known about its causes, full affects, and diagnosis and treatment methods. With multiple definitions and differing diagnosis criteria, there are too many possibilities and grey areas surrounding PCOS. There is a need to change how PCOS is approached in diagnostic methods, with the 2003 Rotterdam criteria potentially proving to be obsolete in successful diagnosis. It is suggested that the use of serum-AMH would provide a better and more universal tool in the diagnosis of PCOS.

Across several studies the success of serum-AMH as a substitute for antral follicle count (the physical counting of antral ovarian follicles, within each individual ovary, via transvaginal ultra-sonographic imaging) or AFC, in the diagnosis of PCOS. In a study conducted by Dewailly et al. in 2011, a most commonly used threshold and methodology system was developed for the use of AMH over AFC [1]. Collecting data from 2008-2010 from a pool of 240 patients referred to the researcher' department, Dewailly et al. paved the way for drawing the Rotterdam criteria into question. The team divided the 240 participants into three groups, i) the non-PCOS group, as a control, ii) a group consisting women that display only Hyperandrogenism (HA) or only Oligoamenorrhea/Oligoanovulation (OA), being either mild or under the presumption of having PCOS, and iii) a group consisting women having been genuinely diagnosed with PCOS. Using a receiver operating characteristic or ROC curve, the following were determined from the aggregate of collected data: the threshold of follicle counting was determined to be 19, with a sensitivity of 81 percent and a specificity of 92 percent. In the same order, data for ovarian volume is as follows: 7ml, 87 percent, and 89 percent. Lastly, using serum-AMH, the threshold was set at 35pmol/l, sensitivity at 92 percent and specificity at 97 percent. These findings suggest that serum-AMH appears to be both a sensitive and specific method, which is also easier to reproduce from one case to another than using the Rotterdam criteria's method of follicle counting. Due to serum-AMH being closely related to markers of HA and ovulatory disturbances, and the pitfalls on follicular counting (heavily dependent on machine quality and/or the skill of the operating technician), serum-AMH would allow for a simplification in PCOS diagnosis, based upon these findings. The findings here have become pinnacle in subsequent related studies, and in many cases are even mirrored in statistically similar results.

In a 2013 study by Casadei et al. [7] similar results were experienced. Using patients referred to the Infertility Center, Section of Gynecology and Obstetrics, Tor Vergata University Hospital, Rome from October 2007 through June 2010 Casadei et al. [7] chose to exclude individuals from their study who have recorded ovarian cysts/tumors (unlike that of Dewailly et al. 2011). As such, PCOS diagnosis was based upon the National Institutes of Health's (NIH) definition: Presence of OA and clinical and/or biological signs of HA being markers of PCOS (when all other possible pathologies can be excluded). Using 59 women divided into three groups the team collected measurements of many of the same hormones as Dewailly et al. [1]. Under the ROC curve, serum-AMH reached 0.97, with a 95 percent confidence interval and AFC reached 0.93 with the same confidence interval: The best compromise between specificity (95 percent (AMH) and 91 percent AFC)) and sensitivity (95 percent (AMH) and 82 percent (AFC)) were obtained using a threshold serum value of 33pmol/l and an AFC of 13 follicles. Casadei et al. [7] concluded that these statistics were similar to the previous Dewailly et al. 2011 [1] findings, when taking into consideration the differences in population sample size, and therefore their results reinforces the validity of the use of serum-AMH as a substitute for AFC when diagnosing PCOS.

In another study, conducted in 2014 by Lauristen et al. [8] using data collected from 2008-2010 from 863 women employed at Copenhagen University Hospital, Denmark, similar findings to the pinnacle study were found again. Once again similar hormone and serum types were collected, in addition to physical measurements/counting, the difference in this study lies in the division of PCOS phenotypes: In addition to using the Rotterdam criteria and NIH criteria, the use of the Androgen Excess and PCOS Society (AE-PCOS) was also used. Individuals falling into the Rotterdam criteria were divided into four subgroups, A) OA + HA, B) OA + PCOM (polycystic ovary morphology), C) HA + PCOM, D) HA + OA + PCOM: AE-PCOS criteria (group A + group C): NIH criteria (group A). Serum-AMH levels, using the ROC curve, were found to have an AUC of 0.906, with a confidence interval of 95 percent, in properly identifying polycystic ovaries. Under the Rotterdam criteria, the prevalence of PCOS is 16.6 percent of the population. However, the current threshold of ≥12 follicles may need to be revised for potentially not revealing a more realistic representation of PCOS prevalence. When drawing from the foundational research of Dewailly et al. [1] and applying a serum-AMH threshold of 35 pmol/l and a 92 percent sensitivity and a 97 percent specificity to this study population, a more biologically plausible prevalence of 23 percent is revealed, showcasing a pitfall within the Rotterdam criteria commonly used in diagnosis.

In a 2015 study by Alebic [9], Duhamel and Dewailly, using a total of 1032 participants, yet another example of the validity of serum-AMH in diagnosing phenotypic diversity of PCOS cases is presented. The study population was divided into three groups based on ovarian morphology. The same, or similar, hormone and serum levels were collected in this study as in others, in addition to physical examination throughout the study. A steadily average increase in

serum-AMH levels across the five described phenotypes was seen, alongside a AMH/AFC value that increased stepwise, being lower in controls, intermediate in PCOM and PCOS C groups and higher in OA PCOS phenotypes A and D respectfully. These results confirmed previously reported serum-AMH levels among the various PCOS phenotypes (among the other serum and hormone levels collected, including LH, insulin and testosterone). These findings were found to be consistent with previously reported studies on the relationship between high AMH concentrations and follicular fluid in women with PCOS. While Alebic, Duhamel and Dewailly (2015) consider that this study may not be fully representative of the population, they suggest that serum-AMH may have a better instance of homogeneity within the PCOS population for removing possible racial, ethnic, geographic origin, selection bias and other infertility treatments.

Drawing from 262 participants, a 2012 study conducted by Eilertsen, Vanky and Carlsen [10]sought to see if serum-AMH was successful in PCOS diagnosis among women who fall into either the Rotterdam criteria and the AE-PCOS (in this literature AE-PCOS is denoted by PCOS-AES) criteria, as well as testing for a threshold value of AMH for PCOS diagnosis. Eilertsen, Vanky and Carlsen [10] concluded through their statistical analysis that there was a strong positive correlation between AMH and AFC, where at a threshold AMH of 20 pmol/l AMH levels in PCOS-R women showed a sensitivity of 94.2 percent and a specificity of 96.5 percent: AMH levels in PCOS-AES women showed a sensitivity and specificity of 95.2 percent and 96.7 percent respectively. Eilertsen, Vanky and Carlsen [10] concluded that serum-AMH can be used as a substitute for PCOM/AFC and is equally as good among the differing current diagnosis criteria; however, it should not replace PCOM/AFC as a diagnostic tool. Differing from other similar studies, Eilertsen, Vanky and Carlsen [10]also believe that the Dewailly et al. [1] threshold serum-AMH level of 35 pmol/l is too high, and the threshold value should be lowered to 20 pmol/l for having a better sensitivity and specificity.

Previous studies suggest the need to revisit other popular diagnosis criteria (Rotterdam, NIH and AE) for women with PCOS, and replace the traditional tools with those of serum-AMH and AMH/AFC ratios. While threshold values of serum-AMH are debated, the majority of studies deferring to the larger study conducted by Dewailly et al. in 2011 as the standard threshold level [1], there is clearly a reoccurring theme that serum-AMH poses a good substitute, and even a replacement for AFC-based criteria. In addition to providing high levels of sensitivity and specificity, AMH also provides a method that can be better used based on cultural and biocultural differences among women globally– creating a standardization the Rotterdam criteria cannot. The simple truth that AMH provides for a better diagnostic tool for PCOS can be seen successfully in each of the above studies, again, each with slight variance in the threshold definitions, but each concluding that this method is a stronger alternative.

Research Question

Since there is still little known about PCOS and its cause/effect relationship continuum, there is a great need to change how it is approached in a clinical aspect, as well as educational and outreach programs. What is known about PCOS is that any woman can be affected by the multitude of symptoms, regardless of location, ethnicity and age.

This creates a need to change how PCOS is approached in diagnostic methods, with the current 2003 Rotterdam criteria potentially proving to be obsolete in successful diagnosis. The Rotterdam criteria is only as successful as the ultrasonographic tools available, the technicians' ability to use such tools and the individuals' ability to access proper health care services, and lacks proper sensitivity/specificity criteria-therefore not being as flexible as the syndrome itself [4]. Furthermore, the Rotterdam criterion is not as successful in the diagnosis of adolescents and pre- and post-menopausal women [2] for being primarily based upon exclusion and morphology.

While the AMH diagnostic tool may not eliminate the issue of access and properly trained technicians and collection tools, it does open the door for diagnosing PCOS among previously marginalized individuals. This creates the difference between a 6-10 percent [3] and a 14-23 percent [8] diagnosis rate among the global population of women. However, the AMH method is not as widely used or understood, and therefore it is not used as commonly as a diagnostic tool. By collecting ultrasonographic images, various hormone secretion levels, serum-AMH levels and other body measurements (BMI, height, and age), over time and space, the use and understanding of the relationship serum-AMH has to Antral Follicle Count (AFC) can be better seen. Results presented in a pinnacle study suggest 97 percent specificity and 92 percent sensitivity interval for the use of serum-AMH over a 92 and 81 percent interval respectively for AFC [1]. These results further suggest a need to look into the use of serum-AMH over AFC in PCOS diagnosis.Using data collected from 2007 to 2015, and building upon it on a wider, more global scale, the relationship AMH and AFC have can be better understood, and hopefully more widely used as a diagnostic tool. Conducting a new, globally placed study or even drawing upon previously documented, and properly acquired/released medical histories, and building from there, could potentially change the way PCOS is approached.

Furthermore, using an introductory, and anonymous, survey (Appendix A) to gain generalized information on diagnosis methods that would run through the determined survey period:Taking this survey and potentially drawing upon global participants whom would be willing to submit to a comparative analysis of their personal PCOS diagnosis, using the Rotterdam criteria and serum-AMH level methods, could potentially close the gaps in PCOS understanding and methods.

Methodology

In order to better understand, on global terms, differing diagnosis methods and determine which is more reliable and/or suitable for proper diagnosis, an introductory survey, and further information from participants across the globe is needed: The last question asks if each volunteer whom takes the survey wishes to be a part, or potentially be a part, of a larger PCOS study, in which necessary contact information (email, phone etc.) can then be provided by the participants.

This study, both by implementation of the introductory survey and participation in the larger study, will be completely acquired via a convenience sample. Given the sensitive nature of the topic, it can be considered that women, whom are active in awareness, outreach and team-building within the PCOS community are more likely than

others to share information that could potentially change the way PCOS is approached, and therefore be more willing to participate in either or both portions of the study. Based upon the types of tests and potential results, this study is a relational study-comparing the relationship between serum-AMH and antral follicle counting in women with PCOS. Given the time and space spans, this particular study could be considered both a longitudinal study and a cross-sectional study: the early survey phase, if this is the chosen end-point, would be considered cross-sectional in nature, for not extending beyond a singular point in time. Conversely, opting into participating in the full study, participation and the acquisition of results would be considered to fall within a longitudinal study design, for extending potentially months.

In cases of where Rotterdam and serum-AMH test results need to be acquired (where previous tests are no older than 2 years), proper study release forms to participants and their medical professionals will be given in order for tests to be administered: In cases where a participants' insurance (where necessary) will not cover such tests, participants can apply for these costs to be covered, only after they have been administered and a bill can be produced. Potential costs would need to be determined based upon medical costs of having a serum-AMH blood test and/or an ultrasonographic imaging test.

Keeping in line with previous studies, the sample population needed to successfully conduct and analyze this study would be at least 384 participants (in the total study, including both parts). This number is achieved by the following formula calculation:

$$ss = \frac{Z^2 \times (p) \times (1-p)}{c^2}$$

$$ss = \frac{1.96^2 \times (0.5) \times (1-0.5)}{0.05^2}$$

$$ss = \frac{0.9604}{0.0025}$$

$$ss = 384.16$$

Where *ss* represents the sample size needed, *Z* represents the Z-value in which a confidence interval of 95% is represented by 1.96, *p* represents the percentage needed for the sample size, 0.5 being half, and *c*signifying the confidence interval, where 0.05 denotes ±5. Given the final calculation, and the principle of rounding, a minimum of 384 participants would be needed to successfully conduct all aspects of the study. Compared to previous studies, using anywhere from 57 to 1032 participants, isolated in very specific regions, where other questions were being asked, the above sample size seems, not only reasonable, but also relevant to conducting generalizable results on a global scale.

Potential ethical issues would be the personal connection between PCOS and the lead researcher and analyst on the project. This ethical dilemma can be solved by bringing on other researchers and analysts to collaborate on analyzing test results, reporting on them, and making future recommendations for further research or change in the current diagnostic system(s).

Data Analysis

The initial portion, including questions such as ethnicity, continent in which respondents live, current age, age of diagnosis, form of PCOS each individual is identified with, and diagnosis method(s) used at the time of diagnosis, will be conducted, each being given an ID number after having been submitted, used for identification in survey analysis. The last question within this survey will ask if the respondent wishes to be contacted to be involved in a larger PCOS study; if yes further contact information is then needed, again being associated with a specific ID number for positive analysis and connection of results. The answers to these questions can provide a more personal level to the larger question at hand, as well as provide insight into methods used globally in PCOS diagnosis and other demographic information that can be pertinent to the larger study (and certainly when participants agree to further participate in the larger study at hand), such as age and ethnicity.

For those willing to participate in the larger study, information such as specific location, specific age versus age cohorts, and specifics about individual PCOS cases will be collected; In addition both a Rotterdam and a serum-AMH level test will need to be acquired and submitted, using the ID number given to each respondent. Individuals taking oral contraceptives will be omitted from the study, as they change serum-AMH levels in the blood. In addition, individuals taking fertility medications (i.e. metformin or other similar prescriptions) will also be omitted from Rotterdam test results, due to these medications having correlation with reducing the size and number of follicles present on each ovary. Individuals excluded from either the Rotterdam or the serum-AMH level results may still be considered for the other test result, however this is at the discretion of the research team, as numbers can become too skewed: These cases may also be used in separate analyses, rather than the full data set.

Rotterdam criteria test results will be acquired via transvaginal ultrasound techniques, where antral follicles between 2- 9mm in diameter, or having an ovarian volume over 10 ml be notated in relation to which ovary they are seen on, and the total number of each ovary be presented. In cases where the individual conducting the ultrasound is unsure of a particular follicle meeting these requirements, these too will need to be notated and later determined as to whether or not they meet them. Copies of medical personnel's notes and ultrasounds are to be sent confidentially to the research team, with the participants ID number in place of personal identifiers, and will later be correlated with other information given using this ID number. Serum-AMH levels are to be collected via blood samples and results are to be sent to the research team in the same manner of the ultrasound and notes. These levels can be more indicative of PCOS indicators than those of the Rotterdam criteria, if serum levels surpass 35pmol/l [11].

Once these results are received, ultrasounds and serum-AMH levels will be put together with their proper associated ID numbered surveys. Upon all results being properly associated with their proper material, an AMH/AFC ratio will be conducted to determine the relationship between serum-AMH and antral follicle count can be measured: This is important in testing whether serum-AMH is a better substitute for AFC, posing implications for being a better predictor of AFC independent of PCOS and PCOM, than using AFC alone can. In addition to this ratio, value/answer means, medians, modes and ranges will also be conducted in order to round the data sets. A t-test

will also be conducted to test the similarities or differences between serum-AMH and AFC in the real world versus the study population. Lastly, an ANOVA test will also be conducted in order to better understand the variations between groups within the study (i.e. age cohorts, ethnicity and country of origin/residence) [12].

The validity and reliability of the study will hopefully find itself to be consistent with previous studies; just on a larger and more global scale, and will potentially prove to be statistically sound. The potential findings and implications of the study population to that of the larger population can prove to be general enough to have significance on a larger scale, as well as specific enough to be applied to the sample size itself.

Conclusions

This proposed study does face certain limitations. Certainly, having a statistically significant number of participants drives the largest limitation of conducting this study. Furthermore, while PCOS can be detected as early as 13, this study eliminated the age cohort of 13-17, also eliminating the need of additional consent information: This elimination can cause a skew in results, and potential limitations on the generalizability of the results as well. However, given the use of a proper standard deviation, margin for error, and confidence intervals, this too could be controlled for on some level.

PCOS presents itself as a rising, and critical, condition in women's health, worldwide. It does not discriminate over age, ethnic origin, or currently residing location: It can be both genetic and environmentally instigated, and can cause slurry of associated health concerns [12]. As such, PCOS presents itself as a major concern to, not just women globally, but to the global health care, and public health communities. Furthermore, early diagnosis and prognosis of PCOS can lead to overall better health outcomes among women with PCOS-diagnosing sooner, and more effectively, can reduce early onset diabetes, heart disease, and obesity. Intrinsically, cementing serum-AMH as a better diagnostic tool would allow for overall better health and understanding of PCOS and the women with whom suffer from it.

References

1. Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, et al. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. Hum Reprod. 2011; 26: 3123-3129.
2. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J ClinEndocrinolMetab. 2013; 98: 4565-4592.
3. Chapman-Novakofski K. Polycystic ovary syndrome. 2016. Magill's Medical Guide (Online Edition).
4. Dewailly D. Diagnostic criteria for PCOS: Is there a need for a rethink? Best Pract Res ClinObstetGynaecol. 2016; 37: 5-11.
5. Loh JS, Maheshwari A. Anti-Mullerian hormone--is it a crystal ball for predicting ovarian ageing? Hum Reprod. 2011; 26: 2925-2932.
6. La Marca A, Broekmans FJ, Volpe A, Fauser BC, Macklon NS. Anti-Mullerian Hormone (AMH): what do we still need to know? Hum Reprod. 2009; 24: 2264-2275.
7. Casadei L, Madrigale A, Puca F, Manicuti C, Emidi E, Piccione E, et al. The role of serum anti-Müllerian hormone (AMH) in the hormonal diagnosis of polycystic ovary syndrome. GynecolEndocrinol. 2013; 29: 545-550.
8. Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. Hum Reprod. 2014; 29: 791-801.
9. Alebic MS, Stojanovic N, Duhamel A, Dewailly D. The phenotypic diversity in per-follicle anti-Mullerian hormone production in polycystic ovary syndrome. Hum Reprod. 2015; 30: 1927-1933.
10. Eilertsen TB, Vanky E, Carlsen SM. Anti-Mullerian hormone in the diagnosis of polycystic ovary syndrome: can morphologic description be replaced? Hum Reprod. 2012; 27: 2494-2502.
11. PCOS Awareness Association. 2016.
12. Garg D, Tal R. The role of AMH in the pathophysiology of polycystic ovarian syndrome. Reprod Biomed Online. 2016; 33: 15-28.