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Role of Antimullerian Hormone as an Early Predictor of PCOS in Perimenarchal Girls-Role in Preventing Associated Comorbidities

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Short Communication

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Short Communication

PCOS (poly cystic ovary syndrome) is an extremely common disorder which even if one applies the most rigid diagnostic criteria one ends up finding 1 in 10 women in the world having this condition. Despite one finding it most commonly during the reproductive age, one also knows that PCOS represents a complex genetic trait that causes lifelong changes. Still the impact along with how it presents in extremes of age i.e. peripuberty and post menopause is not that well understood. It is important to realize that studying these women with their increase in age is pivotal to recognize the risk in those women along with impact on public health and utilize the preventive approaches for their associated comorbidities like type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and related cancers. Studying the younger individuals that get affected is key to understand the earliest markers and probably the factors that to begin with determine the development of the disorder.

Currently Crisosto, et al. [1] studied daughters of ladies with or without PCOS cross-sectional that were in early post menarche (i.e mean menarchal age, 12years). Earlier Sir-Peterman et al. [2] had worked on assessing the development of PCOS in the very beginning of the development where an approach of identification at the earliest period that was feasible for recognizing young females having incipient PCOS by studying the daughters of women with and without PCOS [2]. Although the two populations, just identify study group comprising of girls destined to develop PCOS or those that will not develop PCOS but important to consider is that this group might have an important overlap, these researchers managed to use this approach successfully in finding the early markers and dysfunctions that is associated with this problem. One of the earliest changes appeared to be an increase in basal and stimulated insulin levels that suggests that there Is an initiation of metabolic dysfunction which was associated with an enhanced levels of anti mullerian hormone (AMH).

Similarly the group of Sir Petermann T [3] and Crisosto N [4] had described various early metabolic and reproductive markers of the syndrome that may get modified via interventions which improve adverse pregnancy environment present in PCOS women. Besides that earlier Ibanez, et al. [5] also found this same sequence of metabolic abnormalities that preceded the onset of hyperandrogenism in girls with premature pubarche.

Crisosto, et al. [1] found that daughters of women having PCOS had greater testosterone (T), free androgen index, along with 2-hour insulin, AMH, modified Ferriman-Gallwey scores and ovarian volumes. As far as the subgroup that underwent leuprolide acetate (LA) stimulation, daughters of women having PCOS had

greater LH levels both before and following stimulation along with LH: FSH ratio. Importantly, LH levels positively correlated with both AMH and T levels.

Thus Crisosto, et al. [1] findings imply two important factors which need a more detailed examination. Firstly it might be possible that circulating AMH might be a useful early marker of PCOS that will ultimately develop, that might probably help in trying to take action earlier? Secondly, is it possible that the AMH-LH relationship observed implies an underlying abnormality in the neuroendocrine feedback which gets programmed in utero as per the suggestion of the researchers?

According to Crisosto, et al. [1] the answer to their first question is ''maybe, yes'' and the second ''maybe, no''. These need to be discussed one by one. Sir-Peterman, et al. [2] had earlier shown that the mean AMH levels in daughters of women having PCOS were higher in earlier infancy i.e. 2-3 months of age, which continue to rise throughout the pubertal development, as was compared with controls. But what Is important that needs concern is the marked overlap in AMH values between daughters of control and that of PCOS women. Moreover one needs to follow these daughters in the longer period in the ones who did develop or did not develop PCOS in the adulthood. In another study Villarroel, et al. [6] showed that AMH had a low accuracy for PCOS as far as adolescents were concerned, though the study of AMH isoforms like proAMH, $AMH_{N,C}$ might give a better predictive value. Hence many further studies are required to confirm that AMH alone or along with other indicators, might serve as an accurate sign of incipient PCOS. Wichel et al. [7] gave the criteria of diagnosing PCOS during adolescence.

As far as the second question Crisoto, et al. [1] observed that of late there has been lot of interest arising in response to animal model studies, regarding the possibility that PCOS is the result of in utero fetal programming, which is potentially a response to the high AMH, high androgens or metabolic dysfunction found in pregnant women having PCOS. As per the authors observations this excitement is highly unwarranted and not supported by the epidemiological data available currently. As per Azziz R [8] this small comment is not sufficient and one needs to consider the hypothesis that PCOS is a consequence of genetic programming, which is quiet separate from the genetic programming [8].

Studies done in twins along with familial clustering suggest that there is a very high incidence of heritability. But at present the genetic variants have been separated, at-least by genome wide association studies (GWASs), that appear to represent <=10% of this disorder's inheritance. With the genetic factors not accounting it has been thought by various investigators that the fetal environment plays an important role in the development of PCOS as per the developmental origins of health and disease (DOHaD) hypothesis [9]. But what is important is till date one has not been able to find the genetic factors which possibly help in the development of PCOS.

Importantly GWASs are more suited for finding the common variants that affect over 5% of a population, which has a modest effect instead of the less common variants which have a much greater effect. Additionally GWAS points to loci and not genes? Thus one needs fine mapping of known loci, which may detect particular genes and functional variants that are of interest. Still other genetic factors have not been tested, that include the genomic structural differences along with epigenetic dysregulation. Further currently most GWASs have clustered the many phenotypes of PCOS, and hence there is heterogeneity of populations studied, which decreases the genetic factors specific for particular phenotypes. Even after best work put in worldwide GWASs in PCOS remain few and are small relatively.

Since the genetic factors behind PCOS have not been found most of the researchers have moved towards intrauterine environment to get any idea what is the underlying cause behind PCOS development .Still if one looks at conditions

Which change the intrauterine environment for ways which simulate the pregnant uterus with PCOS, limited data in humans regarding role of intrauterine environment in having any important role in the progeny? Like metabolic stress reflected intrauterine as a small for gestation fetus, has been suggested as a probable risk factor PCOS. Yet larger group studies of PCOS women have not shown an increased prevalence of change in birth weight in women with PCOS [10].

Similarly, an androgenic intrauterine environment has been suggested to cause an increased risk of PCOS. Like women presenting with classic adrenal hyperplasia, who experience hyperandrogenism in utero, seem to show PCOS-like features as an adult, although the degree to which these abnormalities are secondary to persistent postnatal hyperandrogenism and hyper progesteronemia or iatrogenic glucocorticoid excess still remains unclear. As an alternative, prevalence of PCOS was not different in

women who were the product of opposite–sex twin pairs, versus those born of same sex twin pairs, singleton sisters or spouses. This points that increased in utero androgen exposure of a female fetus caused by a shared intrauterine environment with a male fetus, does not result in PCOS like traits [11].

Also importantly in pregnant uterus with PCOS circulating AMH levels are increased. These findings suggest that that in utero AMH excess may cause PCOS like features in their progeny, although human epidemiologic studies still do not exist.

As a whole, human findings supporting the role of intrauterine factors in the genesis of PCOS are still not present. Basic problem is it is difficult to separate the fetal impact of a feature which is a part of the maternal phenotype (like excess AMH, hyperandrogenism or metabolic dysfunction) from that of genetic factors. The 2nd factor is that although a lot of weight has been given to animal studies, insufficient study of the disorder's epidemiology in humans has been carried out, which could help in clarifying the role of intrauterine factors in PCOS [8].

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