Chapter

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# Unveiling the Origin of PCOS

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Polycystic ovary syndrome (PCOS) is a widespread reproductive disorder that encompasses many associated health conditions and has an impact on various metabolic processes. Despite increasing incidence of PCOS, there are several aspects that remain ambiguous. Currently, there is no consensus on the origin of PCOS. In this review; the past, the current and the possible future perspectives regarding the origin of PCOS will be discussed. A better insight into the early origins and natural history of hyperinsulinemic androgen excess may sharpen the perspective of PCOS prevention.

## ANCIENT MEDICAL RECORDS

PCOS has an ancient genetic stamp and references to the syndrome that go back as far as the ancient Egyptian papyri and shown up repeatedly in ancient Greek and Hebrew literatures as well as the medieval and Renaissance periods. These ancient literatures have described PCOS like phenotype in their own peculiar ways.[1]

Here are some of the descriptions from these literatures:

*"But those women whose menstruation is less than three days or is meagre, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant."*

*"Sometimes it is also natural not to menstruate at all... It is natural too in persons whose bodies are of a masculine type... we observe that the majority of those not menstruating are rather robust, like mannish and sterile women."*

*"...there are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman's nature tends to be transformed to the nature of a man, this does not arise from medications, but is caused by heavy menstrual activity."*

*"Many women, when their flowers or tearmes be stopped, degenerate after a manner into a certain manly nature, whence they are called Viragines, that is to stay stout, or manly women; therefore their voice is loud and bigge, like unto a mans, and they become bearded."*[1]

These statements made over a period of more than two millennia describing a combination of symptoms, including menstrual irregularity, masculine habitus, subfertility and obesity are suggestive of PCOS existence during ancient times and was sufficiently common too, to merit description.[2]

Our ancestors described it as a 'fertility problem', but at the same time surprisingly it was also considered a 'survival factor'. Though they were unable to explain the reason, people with insulin resistance survived better when food was hard to get and everyone had to work hard physically to create shelter and stay safe.[3] Now we also understand that PCOS is associated with insulin resistance that actually imparts a relative 'fuel efficiency'; an advantage in times of food scarcity.

In present scenario as food is easily available and one does not have to struggle

hard physically to get it; the obesity, diabetes, heart disease and other PCOS-related complications have no more left PCOS as a 'survival factor'!

## EVOLVING RESEARCHES TO KNOW THE ORIGIN OF PCOS

### The Concept of 'Prenatal Androgen Excess'

Way back in 1982, Goy and Robinson experimented on animal models; the rhesus monkey and sheep and showed that animals exposed prenatally to an exogenous excess of androgens had ambiguous genitalia, fetal growth restraint, virilized behavior and emergence of PCOS-like phenotype including hyperinsulinemic androgen excess, polycystic ovaries, elevated levels of circulating LH, dyslipidemia, visceral adiposity, and reduced ovulation rate particularly in overweight adults.[4–6] With such consistent evidences, the concept of 'prenatal androgen excess' came into view. In year 1989, Hickey *et al* tested the 'prenatal androgen excess' hypothesis for the first time in humans.[7] They performed a longitudinal study of 244 unselected girls recruited prenatally along with their mothers to test maternal androgenemia (through pregnancy) and fetal androgenemia (at birth) into the Raine cohort; initiated by John Newnham and followed them till the age approximately 15 years to be diagnosed with PCOS by NIH or Rotterdam criteria. The authors concluded that their findings did not support the hypothesis of 'prenatal androgen excess'.

However, for many reasons, it was too premature to abandon this hypothesis completely with the possible probability of missing a brief window of maternal or fetal androgen excess by the researchers. Additionally, the applied PCOS definitions might not be valid for 15-yr-old adolescents and thus may have been misleading.

Later in years 1998 and 2002, studies by Padmanabhan and co-workers in sheep and by Abbott and colleagues in the rhesus monkey again affirmed that animals exposed to high levels of androgen *in utero* (by giving very large doses of androgen to the mothers) developed as adults with disrupted ovarian cycles, abnormalities of early follicle development, metabolic abnormalities including insulin resistance and impaired glucose tolerance, mimicking PCOS.[3, 5–6, 8–12] Thus, the hypothesis of androgen programming *in utero* or during postnatal development as an important aspect in the origin of PCOS again gained currency.

However, doubts on the plausibility of this hypothesis persisted and many questions remained unanswered. Because the fetus is buffered against maternal androgen excess in human pregnancy due to the twin barriers of high levels of SHBG and placental aromatase activity, androgen of mother is hard to cross the placenta unless compromised placental function, such as placental aromatase deficiency, stress or inadequate diet is there.

So the question arose, from where does the excess fetal androgen come from and when and how are its effects exerted? And secondly, why PCOS women do not have ambiguous genitals?

The explained hypothesis says that it is not the maternal androgen excess that affects the fetus but the presence of genetically predisposed fetal ovaries or adrenal cortex or both hypersecrete androgens during fetal life or during infancy or during reawakening of the hypothalamic-pituitary-gonadal axis during puberty[13–16] causing hyperandrogenemia and their consequences.

Prenatal androgens produced during fetal organ differentiation are also described as potent gene transcription factors that permanently enhance gene expression (including increased serine phosphorylation of the cAMP response element) related to insulin resistance and hyperinsulinemia.[17] A recent study by Abbott and others done in 2011 in the rhesus monkey also suggested that developmental programming by prenatal androgen exposure

involves epigenetic regulation.[18] It is, therefore, feasible that fetal androgen excess in human females simultaneously reprograms multiple organ systems that will later manifest the heterogeneous phenotype of PCOS.

One of the recent publications that looked in detail at both reproductive and metabolic consequences of androgen excess in rodent model has shown the findings of enlarged adipocytes and decreased serum levels of adiponectin similar to those in women with PCOS, depicting the relationship between excess androgen, obesity and metabolic dysfunction.[19–21]

Virilization of female genitalia, as a result of excess fetal androgen, does not occur in women with PCOS. Prenatal androgen excess does not cause virilization in humans because it has been found to exert subtle but permanent effects on female physiology only.[16, 22]

It has also been shown that cultured human theca cells from polycystic ovaries produce 20 times more androstenedione than similar cells from normal ovaries.[23] The exaggerated ovarian androgen response to exogenous human chorionic gonadotropin (hCG) or endogenous gonadotropins due to increased mRNA expression for many steroidogenic enzymes.[24–27] The genes encoding steroidogenic enzyme were identified in the promoter region of CYP11a.[28] But at the same time, it is unlikely to be the exclusive cause of PCOS because the complex PCOS phenotype seems hard to believe to be due to a single gene defect only.

Prenatally androgenized rhesus monkeys and ewes also have abnormal LH secretions; that is described to be due to permanently diminished hormonal negative feedback on the hypothalamic–pituitary axis during gestation as well as post-puberty. During intrauterine life, this fetal pituitary LH individually or along with placental hCG and genes regulating folliculogenesis and steroidogenesis further result in fetal ovarian hyperandrogenemia leading to prenatal androgen excess and its potential consequences.

In post-pubertal period, abnormally raised LH predisposes the girl to adiposity (basically central) exaggerating insulin resistance. The resultant hyperinsulinemia synergistically interacts with LH hypersecretion to alter ovarian steroidogenesis, premature arrest of follicle development, anovulation and polycystic ovaries.

The similarity of reproductive and metabolic phenotype between prenatally androgenized sheep, or monkeys, and women with PCOS provides strong supportive evidence for intrauterine developmental programming being important in the etiology of PCOS.

## The Concept of 'Adipose Tissue Expendability'

The 'adipose tissue expendability' hypothesis, recently proposed by Virtue and Vidal-Puig, explains the apparent paradox that insulin resistance may occur not only in obese but also when there is a deficit of adipose tissue.[8, 29] The concept says that metabolic health is maintained till the subcutaneous adipose depot can accommodate the caloric supply safely without causing lipotoxicity. When the subcutaneous adipose tissue has a limited capacity to increase its mass safely like in non-obese PCOS women, the adipocytes become overfilled even with the slight fat excess and a lipotoxic state along with dyslipidemia occurs. Lipid starts getting deposited in non-adipose organs such as liver, muscle, or pancreas adversely affecting the metabolism, most notably the insulin action. The concept thus implies that there is an individual set point of subcutaneous lipid storage beyond which lipotoxicity occurs and explains sporadic development of PCOS in women either non-obese or obese.

In obese women with PCOS, obesity exhausts the normal capacity to store subcutaneous fat leading to lipotoxicity and its metabolic complications including hyperinsulinemia, androgen excess, and thus PCOS.[30] Non-obese women who have PCOS

may have lesser subcutaneous fat storage capacity putting them under risk of lipotoxicity and insulin resistance. Such non-obese adolescents with PCOS respond better to insulin sensitizers like metformin, pioglitazone, or their combination with flutamide without the need of lowering body weight.[6,10,12] Adipose tissue expendability concept of PCOS thus emphasizes individually tailored therapeutic weight loss with an aim to reduce the weight until a woman's maximal fuel storage capacity remains there.

Girls with a history of low birth weight and precocious pubarche (appearance of pubic hair before age 8 year) have been found to be at risk for developing hyperinsulinemic androgen excess.[3,11] Accordingly, an increment of weight gain in early life may be among one of the effective approaches to prevent PCOS in later life. Accelerated expansion of adipose tissue before birth and in early infancy has been described to confer protection against developing PCOS in adulthood, perhaps by augmenting the recruitment of subcutaneous adipocytes and hence adequate capacity to store fat.[18] Thus prepubertal and pubertal metformin therapy in girls, who were low birth weight and developing precocious puberty, seems rationale to prevent the development of PCOS during adolescence.[31] But advocation of such preventive insulin sensitizer therapies needs much more robust evidence.

The adipose tissue expendability hypothesis also partly explains the ethnic variation of PCOS and the rationale of how better capacity to store subcutaneous fat make the women escape from developing hyperinsulinemia and androgen excess. Caucasian background confers more subcutaneous capacity for fat storage than a South Asian or Far Eastern origin and so more avoidance of developing PCOS. Indian, Chinese, and Japanese women tend to develop hyperinsulinemic androgen excess and polycystic ovaries at being comparatively lesser overweight than Caucasian women because of ethnically reduced fat storage capacity. More occurrence of PCOS in countries like India, Pakistan, and Bangladesh, where still about one-fourth of the girls have a birth weight below 2.5 kg again can also be explained by this hypothesis.

The linkage between the two hypothesis of origin of PCOS, ***The concept of 'prenatal androgen excess'*** *and* ***The concept of 'adipose tissue expendability'***, seems to exist as testosterone and dihydrotestosterone are known potent inhibitors of adipogenic differentiation of preadipocytes into adipocytes,[13] the females exposed to prenatal androgen excess could have reduced subcutaneous adipogenesis and adipocytes with reduced capacity of subcutaneous fat deposition and thus increased risk of lipotoxicity and related metabolic consequences and PCOS.

## The 'Concept of Genetic Association'

The physiological studies fail to tell us whether it is the elevated androgen levels that lead to insulin resistance or insulin resistance leads to hyperandrogenism and polycystic ovarian morphology or they are a result of increased hypothalamic GnRH secretion drives. A better insight into the epigenetics will probably sharpen the perspective of PCOS origin, identification of at-risk girls, prevention and individualization of therapy.

An increasing number of publications infer that genetics is the primary factor of this disease and associated metabolic complications that is further imposed by its sporadic occurrence among both male and female first-degree relatives of women with PCOS. This genetic association theory also explains that positive family history appears to put the women at risk for the development of PCOS and environmental factors alter the clinical and biochemical parameters in only those with genetic predispositions for PCOS.

The clear genetics of PCOS remains unknown but recent studies indicate this

multipronged disease to be a complex familial trait where several genes combine with environmental and genetic factors to provoke PCOS phenotype.[32]

Till now, researchers had believed excess testosterone production by the ovary during prenatal period, infancy and adolescent period as major initial culprit in developing PCOS and hyperinsulinemia. Hyperinsulinemia and hyperandrogenemia have also been said to be highly heritable parameters transmitted probably as mendelian autosomal dominant or X-linked traits, but the genetic studies have not as yet concluded the pattern of heredity.[33–35]

The current genetic studies are now shifting the focus more on polygenic disturbances especially related to gonadotropin alterations, androgen hypersecretions and insulin resistance explaining the gonadotropin alterations as well.

GWAS (Genome Wide Association Studies) are now new avenues in PCOS researches and at the forefront of genetic technologies shedding light on the biological pathways underlying complex disorders.[36] Till date, a few GWAS have been published in the field of PCOS, which have been done in Han Chinese women, Korean women and North European women. The first GWAS in Chinese women identified three novel PCOS susceptibility loci, namely, 2p16.3, 2p21, and 9q33.3, which mapped to the genomic areas of three genes LHCGR, THADA, and DENND1A, respectively.[37] A second GWAS in a larger sample of Han Chinese women confirmed the previously identified loci and revealed association of eight new loci which corresponded to genomic regions, thus total eleven genetic loci were found to be involved in insulin signaling, hormonal functions, folliculogenesis, and T2DM-associated genes in addition to calcium signaling and endocytosis and associated hormonal and metabolic disturbances with PCOS. A third GWAS performed in Korean population identified GYS2 to be significantly associated only with the obese subgroup of PCOS women. Dr Andrea Dunaif's team genotyped nearly 700,000 genetic markers from nearly 9,000 women from the US and Europe, and have identified two new genetic susceptibility regions that appeared to be unique to European women.[38]

Ethnicity has influenced over the diverse phenotype in PCOS. Louwers' group study concluded the existence of a common genetic risk profile for PCOS across these populations with slightly definite variations. Further resequencing and fine-mapping of the loci identified in Chinese GWAS were carried out to verify associations in Caucasian populations with PCOS. These replication studies have established the association of DENND1A variants with PCOS susceptibility, hyperandrogenism and unfavorable lipid profiles in affected women. On discovery of a signal for the FSH gene by Dr Andrea Dunaif, which suggested that along with LH and FSH how it acts on the ovary or how it is secreted, is very important in the development of PCOS. This is a new way of thinking about the biology of PCOS.[37,38]

To conclude, the etiology of polycystic ovary syndrome (PCOS) has been difficult to determine because its features are heterogeneous, and thus its origin also to be heterogeneous. While the GWAS discoveries are throwing new lights on its origin and pathogenesis, they must be confirmed by candidate gene-based replication studies in various ethnic populations. There is no denying that this fast paced field offers immense potential to pinpoint genes affecting the biological processes involved in etiology of multidimensional polygenic disorders like PCOS. Next Dunaif's team have planned to investigate the genomes of women from African ancestry, in order to get better insight into the shared genetic basis for PCOS in that population too. The next years will be very exciting times as groups from around the world come together to further elucidate the genetic origins of PCOS in different continents.

## CONCLUSION

While developmental determinants of PCOS altogether remain yet to be determined, it is difficult to view PCOS as purely developmental or resulting only from intrauterine exposures of androgens or simply as an adaptation gone astray. Unveiling the origin of PCOS till now has revealed multiple unveiled factors yet to be revealed and recognized. These unveiled factors lay down many possible fields of researches in the future perspectives of the syndrome.

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