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REVIEW ARTICLE

Polycystic Ovary Syndrome in Consanguineous Communities: Genetic, Epigenetic, and Clinical Insights

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Abstract

This systematic review draws together current findings from high-impact medical literature to examine whether Polycystic Ovary Syndrome (PCOS) and consanguinity might be linked. Consanguinity - marriage between biologically related individuals - remains common in parts of the world and is known to increase autozygosity. That genetic effect could matter for a complex, multifactorial condition like PCOS, by both exposing recessive genetic variants and shifting overall polygenic risk. In this review, we look closely at PCOS's genetic framework, explore how consanguinity may affect ovarian reserve, and consider evidence from specific populations, along with early insights into possible epigenetic mechanisms. The overall picture suggests a biologically plausible connection: consanguinity seems to intensify familial clustering of PCOS and influence ovarian reserve, even though some studies disagree. For clinicians, this points to the value of detailed family histories and incorporating genetic counselling into routine care. At the same time, the gaps in knowledge are hard to ignore - especially the shortage of large-scale, multi-ethnic studies that could clarify causality and lead to more targeted interventions.

Introduction

Overview of polycystic ovary syndrome (PCOS)

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a global prevalence estimated between 6% and 13% [1]. Even with those figures, the true burden may be underestimated - some reports suggest that as many as 70% of cases remain undiagnosed [2]. Clinically, PCOS represents a spectrum of hormonal and metabolic imbalances. Women often present with irregular or absent menstrual cycles, signs of androgen excess, and ultrasound evidence of multiple ovarian follicles [3-10].

The syndrome is the leading cause of anovulatory infertility, responsible for roughly 70% of such cases [11]. Although PCOS is not purely a reproductive problem. Its reach extends to serious long-term health issues [10,12,13], including metabolic syndrome [14], type 2 diabetes [15,16] , cardiovascular disease [17,18], obesity [19], and an elevated risk of endometrial cancer [20]. Mental health is also affected; depression, anxiety, and negative body image are common, contributing to social stigma [10,12]. Although there is no cure, symptoms can be controlled through lifestyle modification, targeted pharmacotherapy, and, when needed, fertility interventions [21-23].

Definition and prevalence of consanguinity

Consanguinity describes a marital union between individuals who share a biological relationship - second cousins or closer [24,25]. This practice remains embedded in the social fabric of many regions, particularly in the Middle East, North Africa, and South Asia [26,27]. In certain Arab states, first-cousin marriages constitute 25% - 30% of all unions [26]. In Pakistan, prevalence has been recorded at approximately 63% over recent decades [28]. On a global scale, more than 10% of people live in communities where consanguineous marriage is the cultural norm [29].

The motivations behind such unions are often intertwined with cultural, social, and economic priorities

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- from maintaining family property to reinforcing kinship ties and reducing the likelihood of marital disputes [24,26].

However, the genetic consequences are well documented. Congenital malformation rates in offspring from consanguineous unions average about 4.5%, compared with 1% in the general population [30,31], and the incidence of autosomal recessive disorders is markedly higher [32-35]. That the practice remains common despite these risks highlights how deeply rooted traditions can outweigh medical considerations [24]. For public health professionals, this creates a need for culturally informed genetic counselling that balances respect for tradition with clear communication of health implications.

Rationale for exploring the intersection of PCOS and consanguinity

PCOS tends run strongly in families, with twin studies suggesting that about 70%-71% of the risk could be attributed to heritable factors [36,37]. The genetic basis combines polygenic risk with the influence of rare familial variants [37]. Consanguinity increases autozygosity, leading to long runs of homozygosity (ROH) within the genome [38,39]. These regions can unmask recessive variants and alter the distribution of genetic risk for complex traits [40]. The probability of inheriting deleterious rare homozygous single nucleotide variants (SNVs) is estimated to be 10-20 times higher for the offspring of first cousins [40].

When these dynamics meet the genetic architecture of PCOS [41], the result could be a “genetic amplifier” effect [40]: Not the creation of new mutations, but an intensified expression of harmful alleles already present in the family. This might contribute to higher prevalence rates in consanguineous populations, as well as earlier onset, more severe disease phenotypes, or even distinctive genetic subtypes. Understanding these patterns will require targeted studies in affected populations.

The broader impact of PCOS reinforces the importance of this line of inquiry. Beyond infertility [12,10], women with PCOS face substantial risk for metabolic comorbidities [17] such as type 2 diabetes, cardiovascular disease, obesity, and endometrial cancer, along with psychological strain [12,10]. Consanguinity itself has been associated with multifactorial disorders, including metabolic diseases [27,42]. A study in Pakistan noted a consistent link between intrafamilial marriage, higher BMI, insulin resistance, oligomenorrhea, and impaired glycemic control in women with PCOS [43]. These findings suggest that, in some communities, consanguinity may intensify both the reproductive and metabolic components of PCOS - a combination that has clear implications for clinical screening and management strategies.

Genetic Architecture of PCOS and the Role of Consanguinity

PCOS as a complex, highly heritable disorder

Polycystic Ovary Syndrome (PCOS) is a common disorder that affects many women of reproductive age [1]. Its genetic component is strong, as twin studies suggest heritability around 70-71% [36,37]. Families often show clustering of PCOS cases, which supports the idea that genetics plays a major role [12]. Still, genetics does not act alone-environmental and lifestyle factors clearly influence how the syndrome manifests, making it multifactorial [36].

Genome-Wide Association Studies (GWAS) have identified multiple loci linked to PCOS [44,45,41]. Notable genes include DENND1A, THADA, LHCGR, FSHR, and INSR [44,45], which influence insulin resistance, ovarian steroidogenesis, and steroid hormone biosynthesis [36,37]. These findings hint at why PCOS can appear so differently across patients.

Clinically, PCOS is quite heterogeneous. Researchers describe “reproductive” and “metabolic” subtypes, each with distinct genetic backgrounds and hormonal profiles [9,46]. Studies have mentioned complex molecular networks, pinpointing hub genes as CD93, CYBB, DOCK8, IRF1, MBOAT1, MYO1F, NLRP1, NOD2, PIK3R1, and PTER [47]. Other genes implicated include CYP1A1, CYP19A1, ESR1, AR, AMH, AdipoR1, NAMPT, NPY, PTEN, EGFR, and Akt [36,48]. Altogether, this diversity emphasizes why PCOS can present so variably in different women.

Mechanisms: Increased autozygosity and unmasking of recessive variants

One notable effect of consanguinity is increased autozygosity, which means that long stretches of DNA are identical because they come from a common ancestor [40,38,39]. These regions are called runs of homozygosity (ROH).

The implications are important. Higher homozygosity can shift polygenic liability for complex traits. More critically, it may expose rare recessive variants that would normally stay hidden in heterozygous individuals [40]. Whole- genome sequencing shows that children of related parents carry more deleterious rare homozygous SNVs [40]. To give an example: children of second cousins carry about twice the burden, first cousins tenfold, and double first cousins up to twentyfold, compared with children of unrelated parents [40].

While this effect is clear for rare autosomal diseases, its impact on common disorders, including PCOS, is less dramatic [40,49]. For PCOS, consanguinity might mostly matter if rare recessive variants are important for a family’s phenotype. Alternatively, multiple common variants might combine to create a slightly higher risk. This could explain why consanguinity may influence

both the severity and pattern of PCOS differently in different families.

It is also worth mentioning that elevated homozygosity is not only caused by close-relative marriage. Population bottlenecks and endogamy can have similar effects [38]. Understanding the balance between rare and common variants in these populations will be crucial for tailoring counselling and interventions.

Emerging evidence on specific gene associations (e.g., BRCA1)

New research highlights specific gene links in consanguineous populations. In India, a case-control study found an association between BRCA1 mutations and PCOS ($p = 0.045$) [50]. Around 8.2% of PCOS patients carried the rs1555600862 (C > G) variant in BRCA1, which described as a benign mutation. Notably, parental consanguinity was much more common in the PCOS group-49% versus 8.5% in controls ($p = 0.001$) [50].

Although BRCA1 is best known for breast and ovarian cancer risk, these findings suggest it may also affect ovarian function relevant to PCOS. Increased homozygosity could amplify the effect of such variants, especially if combined with other genetic modifiers.

Clinically, this raises the idea that screening for BRCA1 and possibly other DNA repair genes could inform more than just cancer risk. In some populations, this could guide integrated approaches to both reproductive and oncologic health.

Table 1 [36,44,45,37,41,48] summarizes the key genetic factors implicated in PCOS and how consanguinity might alter their expression or penetrance. This serves as a practical reference for researchers and clinicians working with consanguineous populations.

Impact of Consanguinity on Ovarian Reserve

Evidence supporting reduced ovarian reserve

Several studies suggest that parental consanguinity could influence ovarian reserve, which is a key factor in female fertility [51]. In clinical practice, ovarian reserve is usually assessed through markers such as anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) [52].

A particularly notable study by Melado, et al. (2022) examined 2,198 women from the Arabian Peninsula [51]. The findings were striking: even though women from consanguineous unions were, on average, younger than non-consanguineous women, they showed lower AMH ($p = 0.036$) and AFC ($p = 0.003$) levels after adjusting for age [51]. This observation hints that consanguinity may affect ovarian reserve independently of chronological aging, possibly indicating a lower baseline or an accelerated decline.

From a clinical standpoint, this raises important considerations. If consanguinity predisposes women to earlier reductions in ovarian reserve, proactive assessment might be warranted, particularly for those showing menstrual irregularities or difficulties

Table 1: Genetic factors implicated in PCOS with relevance to consanguinity.

Gene/Locus	Known Role in PCOS	Relevance to Consanguinity/Autozygosity
DENND1A	Hyperandrogenism, gonadotropin exocytosis, ovarian function	Part of polygenic risk, variants associated with PCOS susceptibility in various ethnicities
THADA	Energy metabolism, obesity, insulin resistance	Part of polygenic risk, associated with dysfunctions in energy metabolism
LHCGR	Luteinizing hormone/choriogonadotropi n receptor, ovarian function, androgen secretion	Part of polygenic risk, overexpression in PCOS
FSHR	Follicle-stimulating hormone receptor, ovarian function	Part of polygenic risk, variants investigated for PCOS susceptibility
INSR	Insulin receptor, insulin resistance, ovarian androgen production	Part of polygenic risk, under expression in metabolic tissues, overexpression in ovary
BRCA1	DNA repair, tumor suppressor, ovarian function	Specific association with PCOS in consanguineous cohorts, potential influence on ovarian dysfunction
CYP11a	Steroidogenesis (cholesterol to progesterone)	Reported association with PCOS, though replication varies
CYP21	Steroidogenesis (17-hydroxyprogesterone to 11- deoxycortisol)	Heterozygous association with PCOS- like hyperandrogenemia
CYP17	Steroidogenesis (pregnenolone/progesterone to 17-hydroxy forms), androgen levels	Increased expression in theca cells, polymorphism associated with PCOS
CYP19	Aromatase p450, estrogen formation	Lower activity reported in PCOS
AR	Androgen receptor, androgen effects	Mutations/disruptions reported to cause PCOS, on X chromosome
SHBG	Sex hormone-binding globulin, controls sex hormone levels	Lower in PCOS due to hyperinsulinemia, variants investigated
CD93, CYBB, DOCK8, IRF1, MBOAT1, MYO1F, NLRP1, NOD2, PIK3R1, PTER	Various roles (e.g., cytokine production, TNF signaling)	Identified as "hub genes" in recent bioinformatics analyses, causal relationship with PCOS risk

[36,44,45,37,41,48].

conceiving. In other words, it seems that in daughters of consanguineous unions, fertility issues might appear sooner, suggesting a need for early monitoring and potentially earlier interventions.

Conflicting evidence and methodological considerations

Not all studies, however, report the same association. A retrospective cohort study in Oman (2024), which included 414 women, found no statistically significant differences in AMH, AFC, or FSH between consanguineous and non- consanguineous groups [53]. One important caveat is that AMH measurements were not available for all participants, largely due to resource limitations, though AFC and FSH were more comprehensively assessed [53].

These results contrast with earlier studies from Kuwait and Egypt, which reported reduced ovarian reserve in women born of consanguineous unions [54,55]. Such discrepancies highlight the challenges of interpreting observational data. Differences in sample size, definitions of consanguinity, completeness of hormonal assessments, and statistical methods can all influence outcomes [53].

In addition, particular factors to specific populations might play an important role. Even within the Arabian Peninsula, subtle variations in genetics, environment, and culture might affect ovarian reserve [27]. Additional unmeasured factors-such as nutrition, socioeconomic status, or hidden genetic modifiers-could also contribute, and these are not consistently accounted for across studies.

This variability underscores a critical knowledge gap. That is why drawing firm conclusions from observational studies can be challenging and difficult. Moving forward, there is a strong need for international collaboration and standardized research protocols. Ideally, researches would include uniform definitions of consanguinity, consistent phenotyping of ovarian reserve, detailed reporting standards and comprehensive genetic profiling (like autozygosity mapping). Following such approaches would help clarify true biological associations, enable robust meta-analyses, and accelerate understanding of how consanguinity may affect ovarian function table 2 [51,53].

Population-Specific Observations and Clinical Manifestations

Prevalence of consanguinity in PCOS cohorts

In certain parts of the world, consanguineous marriages remain common, and these patterns seem to leave a mark on PCOS prevalence [26,27]. Take the Middle East or South Asia, for example-clinicians there often encounter PCOS patients whose parents were closely related. A study from a Pakistani infertility clinic in 1997 reported that nearly half of the couples struggling with infertility had first-degree intrafamily marriages [43]. That's striking, isn't it? Fast-forward to the more recent Indian case-control study examining BRCA1 mutations, which found that almost 49% of women with PCOS came from consanguineous unions, compared to just 8.5% of healthy controls [50]. The difference was highly significant ($p = 0.001$), clearly indicating that the pattern isn't random [50].

What's interesting here is the potential double-edged nature of this pattern. High genetic homogeneity increases the risk for recessive disorders, yes, but from a research perspective, it simplifies the genetic landscape. With less background variability, rare variants or polygenic interactions may be easier to detect, providing researchers a unique window into the genetic underpinnings of PCOS in these populations [27]. In a way, studying high- consanguinity cohorts could accelerate discoveries that remain hidden in more genetically diverse groups, ultimately shaping population-specific diagnostic tools or targeted therapies.

Influence on phenotypic expression and metabolic comorbidities

Consanguinity doesn't just seem to affect the likelihood of developing PCOS-it might also influence how the syndrome manifests. Populations with a history of intrafamily marriages often see higher rates

Table 2: Key studies on parental consanguinity and ovarian reserve in PCOS.

Study (Author, Year)	Journal	Region	Study Design	Sample Size	Key Findings (AMH, AFC, FSH)	Association with Ovarian Reserve	Noted Limitations
Melado, et al. 2022 [51]	Reproductive BioMedicine Online	Arabian Peninsula	Retrospective observational	2198	Significantly lower AMH ($p = 0.036$) and AFC ($p = 0.003$) in consanguineous group after age adjustment	Associated with reduced ovarian reserve	Women in consanguineou s group were significantly younger, but adjusted analysis controlled for this.
Mohamed M, et al. 2024 [53]	Research Gat e, PMC	Oman	Retrospective cohort	414	No statistically significant difference in AMH, AFC, and FSH between groups	Does not affect ovarian reserve	AMH not tested in all participants due to financial constraints.

of multifactorial conditions, including diabetes, obesity, and cardiovascular disease [27]. Interestingly, these same conditions are common comorbidities of PCOS [17,15,14].

Evidence from a Pakistani cohort shows clear links: higher BMI, insulin resistance, infrequent menstruation, and impaired glycemic control all clustered in women from consanguineous unions [43]. This suggests that the genetic load for metabolic dysregulation may be amplified in these populations. Coupled with PCOS's ethnic variability, it paints a picture where metabolic complications could appear earlier or more severely, especially when compounded by consanguinity [46].

What does this mean clinically? Screening and management need to be proactive rather than reactive. Women from high-consanguinity backgrounds may benefit from earlier evaluation for glucose intolerance, dyslipidemia, and hypertension. Lifestyle interventions and early therapeutic strategies could be critical here-not just to treat disease, but to prevent or delay its onset. Public health efforts could also target awareness, encouraging communities to engage with healthcare systems sooner rather than later.

Epigenetic Insights and Transgenerational Transmission

A new layer: Epigenetic memory in PCOS

Recent research has revealed something quite fascinating: Embryos from mothers with PCOS carry an "epigenetic memory" [47]. This isn't about DNA sequence changes but rather about how genes are expressed. Abnormal histone modifications-like H3K27me3, H3K4me3, and H3K9me3-disrupt critical early embryonic processes, from genome activation to metabolic regulation [56]. Intriguingly, about half of these abnormal signals in Day 3 embryos appear to originate in the oocyte itself, meaning that the mother passes this signal on before implantation [56].

This adds a compelling layer to familial clustering. While we know PCOS is highly heritable [36,37], these epigenetic mechanisms could explain why daughters of affected women often show PCOS traits, even in the absence of gene mutations [56]. It's a paradigm shift, inheritance isn't just about genes; it's about how genes are regulated across generations.

Consanguinity and epigenetic vulnerability

When you consider consanguinity alongside epigenetics, things get even more intricate. Consanguinity can increase the genetic susceptibility for complex traits via autozygosity and rare variant exposure, while epigenetic dysregulation adds another layer of vulnerability. Together, this creates what one might call a "double hit," where genetic and epigenetic risk converge, potentially leading to earlier onset or more severe PCOS.

Animal models support this idea. Mouse studies show that reproductive and metabolic traits can pass across three generations via epigenetic changes, and some of these traits are reversible with dietary methyl donors [57]. For researchers, this suggests that examining consanguineous populations might reveal unique interactions between genetic load and epigenetic modulation, offering clues that could inform new therapeutic approaches. For clinicians, it underscores the value of integrating family history, genetic, and epigenetic insights when assessing risk in daughters of consanguineous unions.

Clinical Implications and Management Considerations

Importance of comprehensive family history

A three-generation family history remains irreplaceable, especially when consanguinity is common [58,59]. Explicitly asking about parental relatedness can help identify women at higher genetic risk for PCOS and associated metabolic complications [24,26]. Even where advanced genetic testing is unavailable or expensive, a carefully collected history can serve as a practical, low-cost screening tool [60,59].

Training healthcare providers in regions with prevalent consanguinity to take thorough family histories-including consanguinity details-is critical. It's a simple yet powerful way to stratify risk, direct interventions early, and guide genetic counselling, often before molecular diagnostics are accessible [61].

Recommendations for early screening and assessment

Given the evidence, clinicians should consider earlier ovarian reserve testing (AMH, AFC) in daughters of consanguineous unions, especially if they show early menstrual or fertility irregularities [51]. Additionally, vigilance for metabolic complications is key-these women may require proactive screening for insulin resistance, dyslipidemia, and hypertension [27,14,16].

The principle here is clear: don't wait for disease to manifest. Early identification allows timely lifestyle and medical interventions, potentially preserving fertility and reducing long-term complications. This approach moves care from reactive treatment to predictive and preventive medicine, which could have a meaningful public health impact in communities with high consanguinity.

Role of preconception genetic counselling

Finally, preconception counselling is essential for consanguineous couples [60,61]. Traditionally, this has focused on Mendelian recessive disorders, but emerging evidence shows that complex, polygenic traits like PCOS must also be part of the conversation [40].

Counselling should evolve from deterministic predictions to probabilistic discussions. Couples should

understand that their children might inherit not only single-gene disorders but also complex risks influenced by genetic load and epigenetic mechanisms. This empowers families with a fuller picture of potential health outcomes, helping them make informed reproductive choices. Genetic counsellors may require updated training to communicate these nuanced risks effectively, integrating both polygenic and epigenetic insights [62].

Knowledge Gaps and Future Research Directions

Limitations of current research

Looking at the current literature, one thing becomes immediately clear: While there are intriguing associations between consanguinity and PCOS, much of the evidence is observational, often relying on relatively small sample sizes. This makes it hard to draw strong conclusions, especially when socio-economic factors, environmental exposures, or lifestyle variables might be influencing the results [53]. Observational studies are informative, but they leave us in a space of uncertainty- we can see patterns, but proving cause and effect remains elusive.

Another limitation is the lack of consistency across studies. Different research groups use different definitions for PCOS, apply varying thresholds for consanguinity, and measure ovarian or metabolic markers in slightly different ways. This makes comparing results across studies difficult and sometimes leads to contradictory findings, such as the disagreement about ovarian reserve between the Melado, et al. study and the Omani cohort [51,53]. Practical issues, like incomplete AMH measurement due to cost constraints, further muddy the waters [53]. Small-scale genetic studies often lack enough power to detect rare variants or subtle polygenic effects, which are precisely the kinds of factors that might be critical in consanguineous populations.

Taken together, these limitations highlight a need for greater standardization in research protocols. International collaboration, consensus on diagnostic criteria, consistent definitions of consanguinity, and robust data collection- including autozygosity mapping- are all steps that could help the field move forward and reduce conflicting results.

Need for large-scale, multi-ethnic studies

To address these gaps, we need large-scale, multi-ethnic studies that integrate advanced genetic and epigenetic approaches. Techniques like autozygosity mapping and polygenic risk scoring can help us untangle the complex genetic architecture of PCOS, especially in consanguineous populations where rare variants may play a larger role.

Interestingly, the very genetic homogeneity in these populations-which increases disease risk-can also be an opportunity for discovery [40,38]. Studying a more genetically uniform cohort can make it easier to detect novel genes or pathways that might be hidden in genetically diverse populations. In this sense, consanguineous populations are not just “at risk”; they represent natural laboratories that could reveal fundamental insights about PCOS biology. This knowledge could ultimately inform precision medicine strategies that benefit women far beyond these specific populations.

Emerging areas of research

One of the most exciting developments is the exploration of epigenetic changes in PCOS. Research has shown that embryos from women with PCOS carry abnormal epigenetic marks-an “epigenetic memory” that may influence ovarian function and metabolic regulation even before implantation [56,47]. This opens the door to interventions that target the underlying molecular drivers of PCOS, not just the symptoms [57].

Other emerging areas include studying the interplay of gut microbiota, metabolic changes, and endometrial function, which could intersect with genetic and epigenetic susceptibility in consanguineous populations.

Understanding these complex interactions could one day lead to personalized preventive strategies, possibly even preconception or early-life interventions to reduce PCOS risk and severity.

Taken together, these avenues suggest a future where research and care move from reactive symptom management to proactive risk prediction and intervention, especially for women at higher genetic and epigenetic risk.

Conclusion

Polycystic Ovary Syndrome (PCOS) is a complex, highly heritable endocrine disorder that affects reproductive, metabolic, and psychosocial health [10,12]. Consanguinity, common in many regions worldwide [26,27], increases the likelihood of inheriting identical copies of genes from a shared ancestor, unmasking rare recessive variants and influencing polygenic risk for complex traits like PCOS [40]. The evidence reviewed here suggests a meaningful link between PCOS and consanguinity: parental consanguinity may contribute to reduced ovarian reserve, though findings are sometimes conflicting [51,53], and it is frequently observed in PCOS cohorts, especially in the Middle East and South Asia [43,50]. Studies on genes such as BRCA1 [50] and the discovery of epigenetic memory in embryos from women with PCOS [47] highlight the intricate genetic and familial factors at play.

Despite these insights, important gaps remain. Conflicting results, small study sizes, and the largely observational nature of existing research limit our

understanding of causal mechanisms [51,53]. Clinically, taking a detailed three-generation family history-including parental relatedness-is crucial for identifying at-risk individuals [58,59]. Early ovarian reserve assessment and careful monitoring for metabolic complications are recommended for daughters of consanguineous unions. Preconception genetic counselling should also consider the subtler, polygenic risks of PCOS alongside traditional Mendelian concerns [62].

Looking forward, large-scale, multi-ethnic studies that integrate standardized phenotyping, autozygosity mapping, and genomic & epigenomic analyses are essential. Such research will help clarify causal pathways, resolve discrepancies, and guide precise, personalized approaches for prevention, diagnosis, as well as treatment-particularly in populations where consanguinity is common [63-109].

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