# Exploring the Association Between Interethnic Unions and Infertility in the Pakistani Population

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**Abstract**

Pakistan, a nation characterized by profound cultural and genetic diversity, has a high prevalence of both consanguineous marriages and, increasingly, interethnic unions. While the genetic risks of consanguinity are well-documented, the reproductive outcomes of marriages between distinct ethnic groups (e.g., Punjabi with Sindhi, Pashtun with Baloch) remain poorly understood. This review synthesizes literature from human genetics, reproductive immunology, and sociology to explore the hypothesis that interethnic marriages in Pakistan are associated with higher rates of subfertility and infertility compared to intra-ethnic, non-consanguineous marriages. We examine potential roles of genetic incompatibilities (Bateson-Dobzhansky-Muller incompatibilities), immunogenetic mismatches, and compounded socio-cultural stressors. This article highlights a critical research gap, as most studies conflate all non-consanguineous unions, and calls for rigorously controlled investigations to clarify these risks.

**Keywords**: Intermarriage, Infertility, Pakistan, Ethnicity, Genetics, Consanguinity

## 1. Introduction

Infertility, affecting an estimated 15-22% of reproductive-aged couples in Pakistan, is a significant public health burden with profound psychosocial implications (Ahmed, H. M et al., 2020). The etiologies are multifactorial and include male factors (e.g., oligospermia, endocrine disorders), female factors (e.g., PCOS, tubal blockages), combined factors, and a large proportion of unexplained infertility (Deshpande, P. S et al., 2019).

The genetic discourse on infertility in Pakistan has been dominated by the practice of consanguinity, with rates exceeding 60% in some regions (Hussain & Bittles, 2004). This practice increases homozygosity, elevating the risk for autosomal recessive disorders that can impair reproductive function (Sheridan et al., 2013). However, Pakistan's population is structured into several major ethnic groups (Punjabi, Sindhi, Pashtun, Baloch, Saraiki, Kashmiri, etc.) that have maintained genetic distinctiveness due to geographical isolation, tribal endogamy, and cultural practices (Ayub et al., 2015 & Haber et al., 2016). This structure creates a unique genetic landscape where, paradoxically, both inbreeding (consanguinity) and outbreeding (interethnic marriage) may present reproductive challenges.

This review posits that interethnic marriages, while reducing the risk of disorders from shared recessive alleles, may introduce a novel set of biological hurdles genetic, immunological, and epigenetic that can negatively impact fertility. Furthermore, these biological factors are often exacerbated by unique socio-cultural stressors. We aim to critically evaluate this hypothesis, separating it from the established risks of consanguinity.

## 2. The Genetic Landscape of Pakistan and Martial Patterns

Pakistan's ethnic groups are not mere cultural constructs; they represent genetically stratified populations. Genomic studies have demonstrated clear distinctions between groups like the Pashtun (who share ancestry with Central Asian populations), the Baloch (with links to West Asian populations), and the Sindhis (who show higher South Asian ancestry) (Ayub et al., 2015 & Haber et al., 2016). This structure is maintained by a strong tradition of endogamy, both within biraderis (clans) and broader ethnic identities (Bhinder MA, et al., 2019).

Marital patterns are evolving. While consanguinity remains high, urbanization, increased education, and migration are driving a rise in interethnic marriages (Abro, A et al., 2017). These unions represent a natural experiment in human population genetics, bringing together previously separated gene pools.

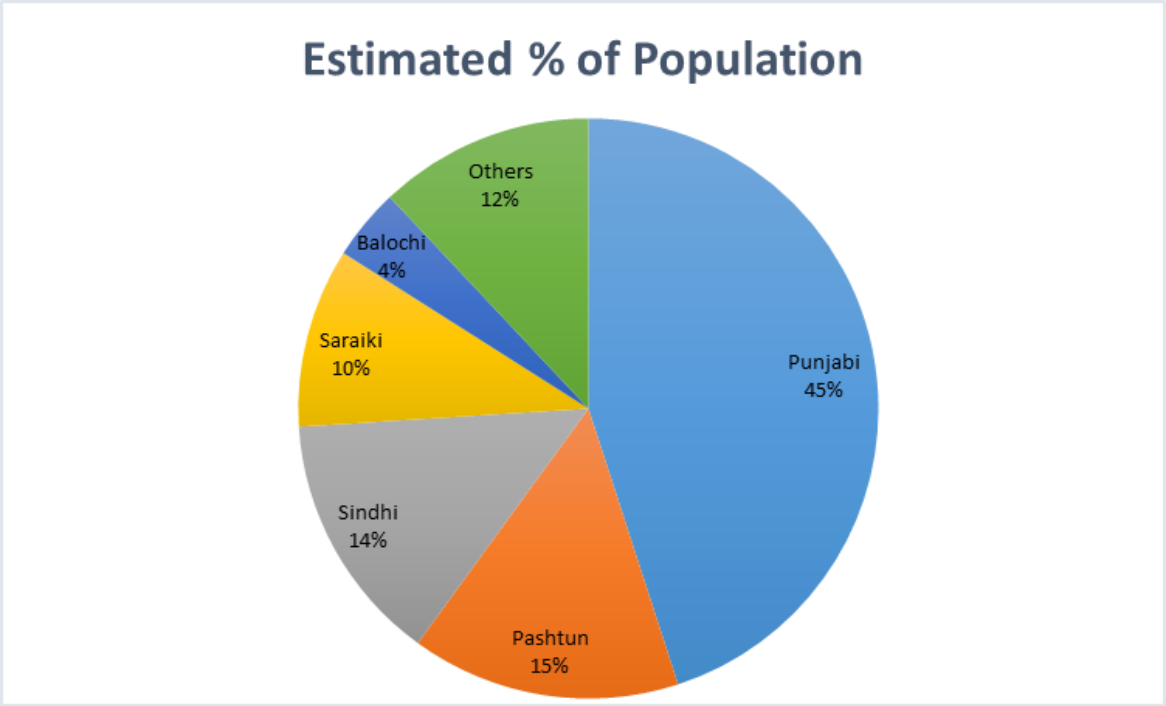


**Figure 1: Major Ethnic Groups in Pakistan and Their Approximate Genetic Affinities** (Ayub et al., 2015 & Haber et al., 2016)

## 3. Potential Mechanisms for Elevated Infertility in Interethnic Couples

### 3.1. Genetic Incompatibilities: Beyond Recessive Disorders

The genetic risks associated with reproduction can be visualized as a U-shaped curve, with risks at both extremes of relatedness.

Consanguinity (Left Side of Curve): Well-understood risk of homozygous recessive disorders affecting reproduction (e.g., congenital bilateral absence of the vas deferens, Kallmann syndrome) (Sheridan et al., 2013).

Interethnic Marriage (Right Side of Curve): Risk of Bateson-Dobzhansky-Muller incompatibilities (BDMI). This model posits that hybrid offspring can experience reduced fitness when alleles that evolved separately in two populations interact negatively post-zygotically (Coyne & Orr, 2004 & Presgraves, 2010). For instance, a sperm-specific protein from one ethnic background might fail to interact properly with an oocyte receptor from another, leading to failed fertilization Similarly,

epistatic interactions disrupting embryonic development could lead to early, often undetected, pregnancy loss (Zheng et al., 2019).

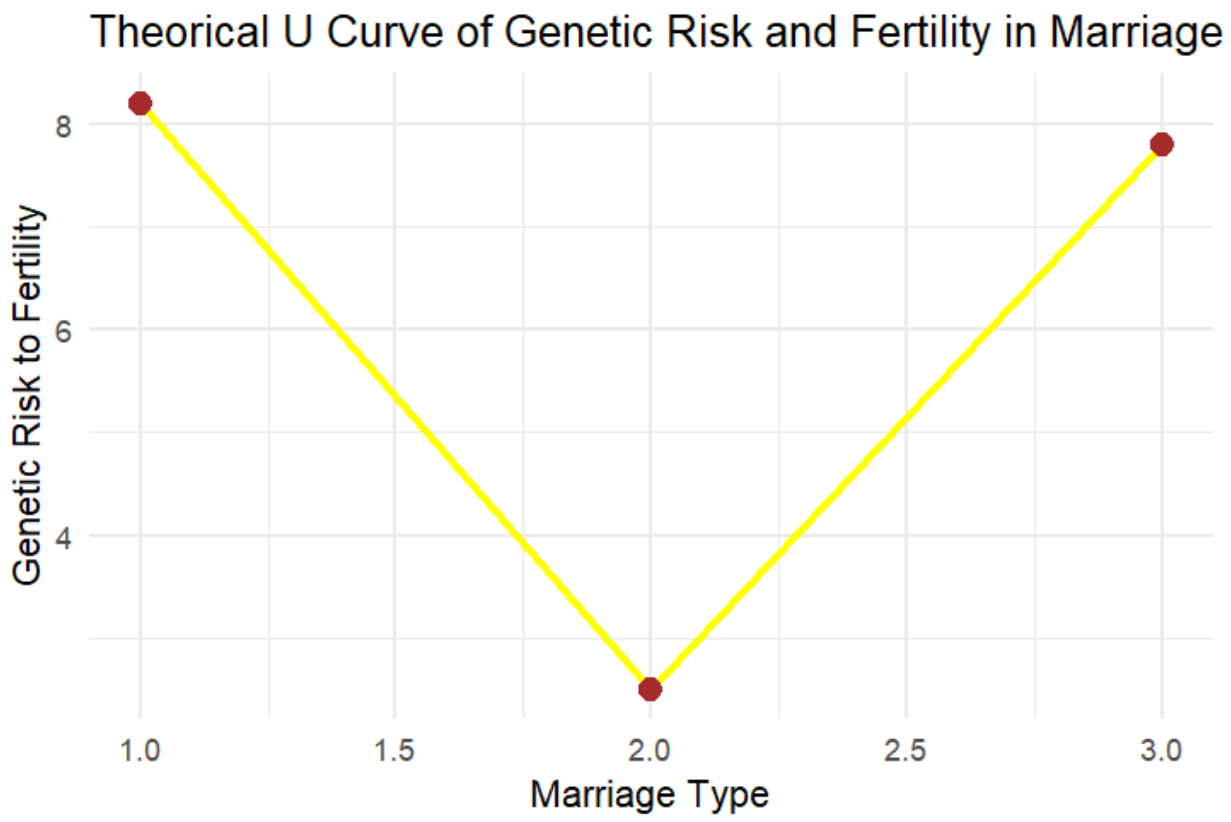


**Figure 2:** Theoretical U-Curve of Genetic Risk and Fertility in Marriage Types

(A simple line graph with Marriage Type on the X-axis (Consanguineous Intra-ethnic -> Non-Consanguineous Intra-ethnic -> Interethnic) and "Genetic Risk to Fertility" on the Y-axis. The line forms a U-shape, highest at the Consanguineous and Interethnic ends, and lowest in the middle for Intra-ethnic non-consanguineous marriages.)

### 3.2. Immunogenetic Mismatches and Implantation Failure

Successful pregnancy requires a delicate immunological dialogue where the maternal immune system must tolerate the semi-allogeneic fetus.

Major Histocompatibility Complex (MHC) and HLA: The Highly Polymorphic Human Leukocyte Antigen (HLA) genes within the MHC are crucial for immune recognition. The MHC-based mate

choice hypothesis suggests humans are attracted to partners with dissimilar MHC genes, potentially providing offspring with broader immune defense (Havlicek & Roberts, 2009; Winternitz et al., 2017). However, extreme dissimilarity, more likely in interethnic couples, could disrupt the precise cytokine signaling needed for trophoblast invasion and placental development (Moffett & Shreeve, 2015). This could increase the risk of impaired implantation, pre-eclampsia, and recurrent miscarriage.

Killer-cell Immunoglobulin-like Receptors (KIRs) / HLA-C Interaction: Uterine Natural Killer (uNK) cells express KIRs that interact with HLA-C on invading trophoblast cells. Specific combinations of maternal KIR and fetal HLA-C genotypes are strongly associated with reproductive success or failure (Moffett et al., 2016). The probability of an unfavorable combination may be higher when parents originate from populations with different frequencies of KIR haplotypes and HLA-C alleles (Parham et al., 2012).

### 3.3. The Compounding Effect of Socio-Cultural and Environmental Stressors

The biological risks cannot be divorced from their context. Interethnic couples often face unique challenges:

Psychosocial Stress: Marrying outside one's ethnic group can lead to social ostracization, family conflict, and a lack of traditional support systems (Hamid, S., *et al* 2011). Chronic stress elevates cortisol levels, which can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, leading to anovulation and reduced spermatogenesis (Lynch et al., 2019 & Nepomnaschy et al., 2006).

Barriers to Healthcare: These couples may delay seeking care because of social judgment, lack of family support, or language barriers when relocating to a new province. (Sami et al., 2022). This delay can turn treatable subfertility into permanent infertility.

Environmental and Lifestyle Changes: Relocation may expose individuals to new pathogens, environmental pollutants, or dietary changes, all of which can subtly influence reproductive health (Mendola et al., 2008).

## 4. Research Challenges and the Critical Need for Data

A significant impediment to confirming this hypothesis is the paucity of targeted research. Most infertility studies in Pakistan categorize marriages only as "consanguineous" or "non-consanguineous," failing to adequately capture the critical variable of interethnic vs. intra-ethnic pairing within the non-consanguineous group (Malik M.I., et al., 2021). This conflation masks potential differences in etiology.

**Future research must:**

1. Collect detailed marital histories that document the ethnic background of both partners.

2. Utilize case-control designs comparing three clear groups: (i) Consanguineous Intra-ethnic, (ii) Non-Consanguineous Intra-ethnic, (iii) Non-Consanguineous Interethnic.

3. Incorporate advanced genomic analyses (e.g., Whole Genome Sequencing) to identify potential BDMI loci and characterize HLA/KIR haplotype combinations.

4. Control for confounding variables (age, BMI, socioeconomic status, duration of infertility, environmental exposures) through multivariate regression models.

**Table 1: Proposed Framework for Classifying Marriages in Future Fertility Studies**

| Category | Definition | Example | Primary Genetic Risk Factor |
|---|---|---|---|
| Consanguineous Intra-ethnic | Partners are blood relatives within the same ethnic group. | Pashtun first cousins. | Homozygosity of identical recessive alleles |
| Non-Consanguineous Intra-ethnic | Partners are not blood relatives but belong to the same ethnic group. | Two unrelated Punjabis. | Standard population risk; lowest risk of genetic incompatibility. |
| Non-Consanguineous Interethnic | Partners are not blood relatives and belong to different ethnic groups. | A Sindhi man and a Baloch woman. | Bateson-Dobzhansky-Muller Incompatibilities; Immunogenetic mismatch. |

## 5. Conclusion and Future Directions

The prevailing narrative of genetic risk in Pakistani reproduction is incomplete. While consanguinity remains a paramount concern, the rising trend of interethnic marriage may be associated with a different spectrum of challenges rooted in genetic and immunological incompatibility, exacerbated by socio-cultural stress. It is imperative to move beyond the simplistic consanguineous/non-consanguineous binary.

The aim is not to stigmatize interethnic unions but to advocate for a more sophisticated and effective approach to reproductive healthcare:

Enhanced Genetic Counseling: Preconception and infertility counseling should include a detailed ethnic history for both partners. Expanded carrier screening panels that include mutations common across all Pakistani ethnic groups should be developed.

Targeted Research Funding: National and international health agencies should prioritize research into the reproductive outcomes of interethnic couples.

Informed Clinical Practice: Clinicians should be aware of the potential for Immunogenetic factors in cases of unexplained infertility or recurrent miscarriage in interethnic couples.

Understanding the intricate interplay between population genetics, immunology, and society is the key to unraveling the complex etiology of infertility and providing compassionate, effective care for all couples in Pakistan.

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**Author Contribution**

N.A composed the manuscript. F.A and M.B collected data. N.A, F.A and W.S performed analyses reviewed and revised the manuscript. W.S conceived and supervised the study. All authors contributed to manuscript preparation, review, and approved the final version of manuscript.

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