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Reproductive Risk in India: Lab Evaluation of Prenatal Screening And IVF-Linked Diagnostics

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ABSTRACT: Infertility is a rising public health issue in India, yet diagnostic practices remain unevenly standardized. This study presents a laboratory-based evaluation of five case studies involving four key diagnostic tools in fertility and prenatal care: Antinuclear Antibody (ANA) testing, Double Marker, Quad Marker, and Non-Invasive Prenatal Testing (NIPT). Using original patient data from an assisted reproductive technology (ART) clinic, the study assessed procedures, interpreted results, and evaluated clinical utility. ANA testing suggested a link between autoimmunity and IVF failure, highlighting the role of immunological factors in implantation. The Double and Quad Marker tests proved to be cost-effective options for early aneuploidy screening but showed moderate specificity. In contrast, NIPT demonstrated high sensitivity and specificity for detecting trisomy, especially when fetal fraction exceeded 4%, making it a reliable tool for prenatal risk assessment. Despite their clinical value, these diagnostics are underutilized due to high costs, limited awareness, and inconsistent regulations. The findings underscore disparities in access and the need for standardized protocols and policy support to improve reproductive healthcare in India. In this case-series, ANA positivity was generally linked with IVF failure, while Double and Quad Marker results remained consistently low-risk. NIPT findings confirmed high reliability when fetal fraction exceeded 4%, demonstrating how these diagnostics function in real-world Indian IVF settings.

KEYWORDS: Translational Medical Sciences, Disease Detection and Diagnosis, Biomarkers, IVF, NIPT.

Introduction

According to the World Health Organization (WHO), reproductive health means that people of all ages should be able to have safe and satisfying sexual lives and make informed choices about if, when, and how they want to have children.[1] Reproductive health is a cornerstone of public health, and in India, improving access to accurate, timely, and culturally sensitive diagnostic services for women remains a pressing challenge.[2]

While maternal health indicators have improved significantly over the past few decades, reproductive health remains a critical concern, particularly for women in India. Among the various issues, infertility has emerged as a growing public health challenge, both globally and nationally. The condition is clinically defined as the inability to conceive after engaging in regular, unprotected sexual intercourse for 12 months or more. Infertility is broadly categorized into two types: primary infertility, wherein an individual has never conceived, and secondary infertility, which is characterized by difficulties in conception following a previous successful pregnancy.[3]

Cultural and Societal Factors Affecting Women's Health:

The experience of infertility is psychologically and emotionally distressing.[4] In many Southeast Asian countries, there is an additional layer of social burden due to deeply rooted societal beliefs and expectations that prioritize reproduction and childbearing.[5] Within such contexts, the inability to conceive may disrupt traditionally ascribed roles and identities, especially for women, leading to further marginalization.

Despite its prevalence, infertility is surrounded by stigma and taboo, which discourages open discussion and limits access to essential support systems. The perception of infertility as a deviation from normative familial and gendered expectations amplifies the psychological toll, often resulting in social exclusion, marital strain, and personal distress.[6]

Widge and Cleland conducted a postal survey with 6,000 gynecologists across India to gain insight into the health services provided and challenges faced in the public sector concerning infertility management. The study revealed that the public sector played a limited role in infertility care. Inadequate infrastructure, lack of information and training, absence of clear protocols at all levels, and private practice by public health doctors were the key problems mentioned.[3]

Government Policies to Address Infertility Issues in India:

With rising infertility rates, the Indian Parliament enacted the Assisted Reproductive Technology (Regulation) Act, 2021.[7] It protects the rights of infertile couples and surrogate mothers, ensuring financial security for surrogates. The Act regulates ART clinics and banks, mandating the ethical and medically supervised handling of gonadal tissues, embryos, and gametes for both clinical and research use. The Indian Council of Medical Research (ICMR) also issued guidelines to ensure ethical and medical compliance.

As ART services expand, *in vitro* fertilization (IVF) has become central to infertility management. The IVF cycle typically involves several stages: controlled ovarian stimulation using hormonal injections, egg retrieval, fertilization in a lab-

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oratory setting, embryo culture, and embryo transfer into the uterus, followed by hormonal support and monitoring to assess implantation and pregnancy outcomes.[8,9]

Accurate and timely diagnostic testing is critical in the IVF process. Tests such as antinuclear antibody (ANA) screening, double and quad marker tests, and non-invasive prenatal testing (NIPT) are increasingly integrated into IVF and prenatal care.

The ANA test detects antibodies that target cell nuclei and can provide insight into autoimmune contributors to infertility. **The Double Marker Test (First Trimester Maternal Serum Screening)**, performed between 9–13 weeks of pregnancy, measures Pregnancy-Associated Plasma Protein A (PAPP-A) and free β-hCG to assess the risk of chromosomal abnormalities. When combined with a nuchal translucency (NT) scan, this test improves early risk assessment for genetic disorders.

The Quad Marker Test (Second Trimester Maternal Serum Screening), performed between 15 and 22 weeks, evaluates four biochemical markers to estimate the risk of chromosomal abnormalities and neural tube defects.

With the increasing availability of such diagnostic tools, there is a growing need to assess their clinical impact, accessibility, and interpretation in real-world practice. These modalities not only provide early risk assessments for genetic and immunological disorders but also guide decision-making during pregnancy and fertility treatments.

IVF-related prenatal screening includes NIPT, ultrasound imaging, and invasive diagnostic procedures. NIPT analyzes circulating fetal DNA fragments in maternal blood to detect chromosomal abnormalities such as Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), Patau syndrome (trisomy 13), and sex chromosome anomalies. Ultrasound examinations provide structural and anatomical assessments, while invasive methods like chorionic villus sampling can directly diagnose genetic conditions.

Despite technological progress, barriers such as inconsistent guidelines, lack of awareness, limited standardization, and socio-economic disparities hinder the effective implementation of these tests in routine reproductive healthcare.

This study seeks to address these gaps by conducting a laboratory-driven investigation rooted in practical diagnostic experiences and supported by original data analysis. The aim is to assess the performance, utility, and limitations of NIPT, IVF-related immunodiagnostics (Figure 1), and prenatal screening tests in Indian diagnostic settings, while also considering broader implications for healthcare providers and policymakers seeking to improve reproductive health outcomes.

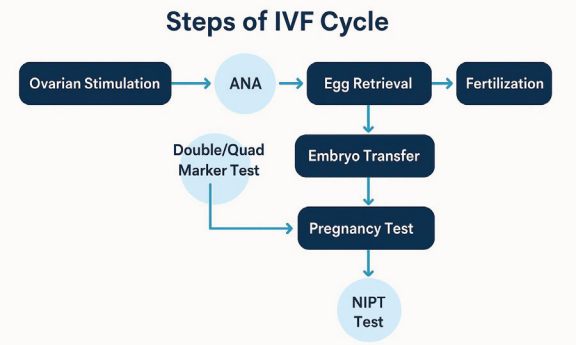

Figure 1: Diagrammatic representation of the stages of the IVF process at which ANA, Double Marker, Quad Marker, and NIPT tests are typically performed, aligned with clinical decision points.

Objectives of the Research:

To learn, evaluate, and analyze key diagnostic methods used in fertility and prenatal care through hands-on laboratory testing and interpretation of real patient data.

Why This Study is Different:

Unlike literature-based reviews, this study integrates personal lab-based experimentation with original clinical data, offering firsthand insights into diagnostic accuracy and real-world applicability.

Methodology

Study Design and Participants:

This was a descriptive case-series analysis of samples from patients (identification was kept anonymous) and laboratory reports obtained from a single diagnostic laboratory. Reports of five patients were selected for each of the following investigations: antinuclear antibody (ANA), first-trimester double-marker screening, second-trimester quadruple-marker screening, and non-invasive prenatal testing (NIPT). Patient identifiers were removed, and each report was assigned an anonymized code (P001–P005). The dataset contained maternal age, gestational age at the time of testing, laboratory values (raw concentrations and multiples of median, MoM), ANA index values, NIPT results, fetal fraction percentages, and IVF outcomes when available.

Sample Collection and Laboratory Analysis:

1. ANA Testing:

Peripheral blood samples were analyzed using an enzyme-linked immunosorbent assay (ELISA) for ANA. The assay was performed according to the manufacturer's protocol (ANAscreen ELISA Assay Kit®, Eagle Bioscience). Optical density was measured at 450 nm on a spectrophotometer. ANA index values were calculated as the sample absorbance/negative control absorbance (Table 1).

Table 1: Parameters for ELISA assay for ANA test. The key analytical parameters used in the ELISA assay for ANA detection, including standard cut-off values.

Parameter	Values / Description
Expected Values	Negative: < 0.9 Borderline: 0.9 – 1.1 Positive: > 1.1
Cut-off Index	1.1 (normal range)

2. Double-Marker Screening:

Maternal serum samples collected between 11–14 weeks of gestation were tested for free β-hCG and pregnancy-associated plasma protein A (PAPP-A). Measurements were performed on Elecsys free β-hCG and PAPP-A assays on the Roche cobas e / Elecsys platform. Raw concentrations were converted to MoM values using laboratory gestational-age medians, with adjustment for maternal weight where applicable.

a. MoM β-hCG > 2.0: high risk for Trisomy 21

b. MoM PAPP-A < 0.5: high risk for Trisomy 21/Trisomy 18

3. Quadruple-Marker Screening:

Maternal serum samples collected between 15–22 weeks of gestation were analyzed for α-fetoprotein (AFP), unconjugated estriol (uE3), free β-hCG, and inhibin-A. Analytes were measured on Roche Elecsys / cobas e (electrochemiluminescence immunoassay), and MoMs were calculated using the laboratory's internal medians. Composite risk scores for trisomies were generated by the lab software, using cut-offs of MoM > 2.0 for β-hCG and inhibin-A, and MoM < 0.5 for PAPP-A and AFP (Table 2).

Table 2: Interpretation of Quad Marker Screening Results using the four biochemical markers measured in the quad test, with clinical implications of high and low levels for each marker in the context of prenatal screening.

Marker	High-Level	Low-Level
AFP (Alpha-fetoprotein)	May indicate neural tube defects (e.g., spina bifida)	May suggest Down syndrome (Trisomy 21)
hCG (Human Chorionic Gonadotropin)	Linked to Down syndrome (Trisomy 21)	May indicate Edwards syndrome (Trisomy 18)
uE3 (Unconjugated Estriol)	—	Can be seen in both Trisomy 21 and Trisomy 18
Inhibin A	Associated with Down syndrome (Trisomy 21)	—

4. Non-Invasive Prenatal Testing (NIPT):

NIPT was performed between 11–13+4 weeks of gestation. The procedure was performed as described by LeFevre & Sundermeyer (2020).[10] cfDNA was extracted from 10 mL maternal plasma collected into cfDNA stabilization tubes, using Qiagen QIAamp™ Circulating Nucleic Acid Kit. Library preparation and sequencing were conducted on the Illumina NextSeq 500/550 sequencing platform. Reads were aligned and analyzed with the laboratory's VeriSeq™ NIPT Analysis Software to detect aneuploidy for chromosomes 13, 18, and 21. Fetal fraction was estimated by the SNP-based method/fragment size distribution method. Samples with fetal fraction < 4% were considered unreliable.

Data Extraction and Analysis:

From each report, the following variables were extracted: patient code, maternal age, gestational age at test, raw analyte concentrations, MoM values, ANA index, NIPT result (positive/negative for trisomy 13/18/21), fetal fraction, and IVF outcome. Data were compiled into summary tables. Given the small sample size (n = 5 per test), results were presented descriptively as counts, ranges, and mean values where appropriate. No inferential statistics were applied.

■ Results

In this study, I have made an effort to bring together my experience of witnessing the diagnosis and interpretation of lab findings for the IVF procedure. I analyzed the reports of 5 patients for each test- ANA, double marker, Quadruple Marker test, and NIPT to understand the procedure involved, sensitivity, and the interpretation of the results obtained. To streamline presentation, all patient results are consolidated into Table 3.

1. ANA Testing: Two of five patients (40%) were ANA-positive (index values: 1.62 and 1.32). One ANA-positive patient experienced recurrent IVF failure, while all three ANA-negative patients had successful IVF outcomes.

2. Double Marker: All five patients screened low-risk between 11–14 weeks of gestation. Mean MoM values were 1.96 for free β-hCG (range: 1.28–3.31) and 1.52 for PAPP-A (range: 0.95–1.92). No abnormal risk scores were observed.

3. Quad Marker: All patients tested between 15–22 weeks were low-risk. Mean MoMs were AFP 1.18 (range: 0.66–1.76), uE3 1.28 (range: 1.14–1.68), β-hCG 1.32 (range: 0.71–2.23), and inhibin-A 1.51 (range: 0.99–2.23). No results exceeded risk thresholds.

4. NIPT: Four patients received negative results for trisomies 13/18/21, while one patient (20%) was flagged as high-risk for Trisomy 21. Fetal fraction values (not shown) ranged from 8.4% to 13.4%, all above the 4% reliability threshold.

Table 3: De-identified laboratory and outcome data from five patients. MoM values are multiples of the median adjusted for gestational age. IVF outcomes reported where available.

Patient ID	ANA Result	Double Marker β-hCG (MoM)	Double Marker PAPP-A (MoM)	Quad AFP (MoM)	Quad uE3 (MoM)	Quad β-hCG (MoM)	Quad Inhibin A (MoM)	IVF Outcome	NIPT Result
P001	Positive	3.31	0.95	2.02	1.65	0.99	1.62	Success	Negative
P002	Negative	1.28	0.66	1.68	1.25	1.84	1.84	Success	Negative
P003	Negative	1.92	1.39	1.14	0.71	1.60	1.60	Success	Positive (T21)
P004	Positive	1.70	1.76	1.25	0.76	1.74	1.74	Recurrent failure	Not applicable
P005	Negative	1.58	1.15	1.06	2.23	1.40	2.23	Success	Negative

■ Discussion

The integration of advanced diagnostics for infertility management in India faces systemic challenges: limited awareness, inconsistent clinical guidelines, socio-economic barriers, and variation in result interpretation. There is a pressing need to evaluate how these tools are being applied in real-world settings and their impact on clinical decision-making in IVF **(Figure 1)**. This study evaluates four diagnostic modalities—ANA testing, Double Marker, Quad Marker, and NIPT—in the context of IVF and prenatal care in India. The findings highlight both their clinical relevance and systemic challenges to implementation.

ANA Testing and IVF Outcomes:

According to the ANA result and respective IVF outcome, the ANA-negative patient successfully conceived, whereas one of the positive cases experienced failed outcomes (Table 3). This pattern aligns with multiple studies showing that ANA positivity is associated with lower oocyte maturation, reduced rate of high-quality embryos, and poorer IVF outcomes, including decreased pregnancy and implantation rates

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and increased miscarriage risk.[11] ANAs are thought to impair both embryo quality and endometrial receptivity, potentially via autoimmune-mediated inflammation.[12] In contrast, ANA-negative results help rule out immune-related causes, allowing clinicians to proceed with standard IVF protocols. For ANA-positive patients, immunomodulatory treatments such as low-dose prednisone, aspirin, or IVIG are sometimes used to reduce inflammation and improve implantation chances, although their benefits remain debated. Our results also showed that in one of the case studies, where the patient was ANA-positive, a successful pregnancy occurred.[11] This could be possible with the use of immunomodulatory treatments. ANA testing is particularly valuable for women with repeated IVF failure or unexplained infertility, as it can guide more personalized management. However, it is not yet part of standard infertility workups in many Indian clinical settings, despite being inexpensive, minimally invasive, and clinically informative.[11]

Double Marker Screening:

All patients screened were low-risk, consistent with the test's utility as a first-line, early, non-invasive screening method for chromosomal abnormalities.[13] When combined with a nuchal translucency ultrasound, the double marker improves risk estimation for Trisomy 21 and 18.[14] However, its moderate specificity increases false positives, necessitating confirmatory follow-up in high-risk cases. Despite these limitations, it remains widely accessible and cost-effective in India, making it a practical option compared with more advanced tests such as NIPT.[15]

Quad Marker Screening:

Second-trimester Quad Marker testing also yielded low-risk results across all patients. While less specific than NIPT, it plays a vital role in detecting neural tube defects—an area where NIPT has limited utility.[16] It is particularly useful in rural and low-resource settings, where first-trimester screening may be missed and NIPT is cost-prohibitive. Despite moderate specificity, its affordability and accessibility make it a staple in India's public and semi-urban healthcare systems.[16]

Non-Invasive Prenatal Testing (NIPT):

These results demonstrate a mix of high-risk and low-risk interpretations, providing a clear opportunity to assess both the negative predictive value (NPV) and the positive predictive value (PPV) of NIPT in a real-world cohort. The three negative cases are clinically reassuring, given NIPT's NPV exceeds 99.9% for common aneuploidies such as Trisomy 21, 18, and 13 (Table 3).[17] The elevated fetal fractions (not shown in the table) in all cases further support the reliability of these results, as fetal fraction is a key determinant of test accuracy. While postnatal outcomes were not available, the lack of reported complications or follow-up interventions suggests confidence in these negative findings.[18] The single high-risk result in this case series (P003) highlights the clinical utility of NIPT as a sensitive screening tool. A fetal fraction of 12.4% ensured adequate representation of cell-free DNA (cfDNA), and the identification of elevated risk for Trisomy 21 demonstrates the test's sensitivity. Existing research indicates that NIPT's sensitivity for Trisomy 21 exceeds 99%, with a specificity exceeding 99.9%.[19] However, the PPV of a positive result varies depending on maternal age, prior risk, and population prevalence. In high-risk groups, such as women of advanced maternal age or those undergoing IVF, the PPV is considerably higher than in the general population.[20] In all the given case studies, the fetal fractions greater than 8% minimize the risk of test failure or inconclusive results. Fetal fraction, which represents the proportion of fetal cfDNA in maternal plasma, is known to directly affect the reliability of NIPT. A threshold of greater than or equal to 4% is typically required for accurate interpretation. Low fetal fraction is associated with reduced sensitivity and test failure and is more common in patients with high BMI, early gestational age, or underlying medical conditions.[21] None of the cases here fell into that category, which strengthens the reliability of the interpretation. Despite its high performance, NIPT is not a diagnostic test. False positives can occur due to biological variables such as confined placental mosaicism, vanishing twin syndrome, or maternal chromosomal abnormalities. Accordingly, clinical guidelines consistently recommend that all positive NIPT results be confirmed via invasive testing, typically chorionic villus sampling (CVS) or amniocentesis, before any clinical decisions are made.[22]

More affordable alternatives to NIPT include first-trimester combined screening (serum markers plus nuchal translucency) and the second-trimester quadruple marker test. While these options are less expensive and widely available, their sensitivity and specificity are lower than NIPT.

While NIPT outperforms conventional serum-based tests, barriers such as high cost, lack of insurance coverage, and inequitable access limit widespread use in India.[23] Genetic counseling remains essential for appropriate patient interpretation of both positive and negative results.[24] Patients must understand that while a negative result is highly reassuring, it does not rule out all chromosomal or structural abnormalities. Conversely, a positive result indicates an elevated risk, not a diagnosis. Counseling plays a vital role in helping patients interpret their results, particularly when follow-up diagnostic procedures are indicated.

■ Limitations

This study has several limitations. The small sample size (n = 5 per test) and descriptive design limit the statistical strength and generalizability of the findings. All data were derived from a single diagnostic laboratory, which may not reflect broader clinical practice across India. The absence of detailed patient demographics, such as IVF cycle number or comorbidities, further reduces the depth of interpretation. In addition, the lack of follow-up outcomes restricts the ability to validate long-term clinical relevance. These constraints highlight the need for larger, multi-center studies with longitudinal data to better assess the role of these diagnostics in improving reproductive healthcare.

Conclusion and Future Perspective

This study highlights the value of integrating immunological and genetic diagnostics into reproductive healthcare in India. Unlike prior literature-based reviews, this work draws on original case data, showing that while ANA-positivity generally correlated with IVF failure, one ANA-positive patient achieved success—an anomaly that both supports and complicates existing findings. ANA testing can help uncover immune-related barriers to successful IVF, while serum-based marker tests remain widely accessible tools for early prenatal screening. NIPT offers superior accuracy for detecting common aneuploidies but remains constrained by cost and inequitable access.

Moving forward, expanding access to advanced diagnostics like NIPT will require supportive policies, wider insurance coverage, and integration into public health programs. At the same time, greater awareness of affordable immunological and serum-based tests can improve baseline infertility and prenatal care, especially in resource-limited settings. Strengthening genetic counselling services is also essential to ensure that patients and clinicians can interpret results appropriately and make informed decisions.

India's reproductive diagnostics landscape is at a pivotal stage: combining low-cost screening with advanced genomic tools, supported by standardized protocols and equitable access, has the potential to significantly improve IVF outcomes and maternal-foetal health in the coming decade. With the Indian women's reproductive health market projected to grow by 6.7% by 2033,[25] these diagnostic advances—if paired with policy reforms—can translate into more equitable and effective fertility care.

Ethical Statement

This study was conducted under the supervision of qualified professionals in a certified diagnostic laboratory. The student did not handle any clinical specimens directly. All sample processing followed institutional biosafety and ethical guidelines, and no personal or identifiable data were used.

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Author

I'm Mannat Oberoi, a Grade 12 IBDP student at The Shri Ram School, Moulsari, passionate about biochemistry and biomedical sciences. This paper builds on my prior research in IVF diagnostics, finding that while all four tests aid fertility care, NIPT is most accurate yet often inaccessible in India.