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Evaluating the Role of Anti-Paternal Cytotoxic Antibodies (APCA) in Recurrent Miscarriage: A Critical Review

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Abstract

Background: Recurrent miscarriage (RM), or recurrent pregnancy loss (RPL), is a significant reproductive health issue that affects approximately 2% to 5% of women attempting to conceive. The anti-paternal cytotoxic antibody (APCA) test can serve as an important diagnostic tool for investigating RM. This study aims to review the existing literature on the prevalence and diagnostic utility of APCA testing in women experiencing RM.

Materials and Methods: The search was conducted across online databases, including PubMed, Scopus, Web of Science, CIVILICA, and Google Scholar until March 2024. This review integrates findings from various studies to determine the prevalence and diagnostic effectiveness of APCA in women with RM.

Results: The incidence of positive APCA was detected in 32% of successful pregnancies. However, the detection of APCA was rare before 28 weeks of gestation, which limits its utility as an early diagnostic tool for recurrent miscarriage. For women diagnosed with RM and positive APCA, immunotherapy may serve as a promising treatment option that can significantly enhance live birth rates, increasing from 18.5% to 53.7% post-treatment. While APCA testing can provide insights into miscarriage risk, its reliability is constrained by methodological inconsistencies and demographic variability. To enhance the accuracy and relevance of APCA testing in clinical practice, it is essential to consider individual patient factors such as age, medical history, and genetic background when developing treatment strategies.

Conclusion: While, APCA testing provides valuable insights into immunological factors related to recurrent pregnancy loss (RPL), but its limitations necessitate a cautious approach. Clinicians should integrate APCA results with genetic assessments and environmental considerations to develop a comprehensive diagnostic strategy for better management of RPL.

Key Words: APCA, Diagnostic, Recurrent miscarriage, Predictive.

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1- INTRODUCTION

Recurrent miscarriage (RM), or recurrent pregnancy loss (RPL), is a significant reproductive health challenge that affects approximately 1-2% of women attempting to conceive (1, 2). RM is not solely a medical condition; it also inflicts significant psychological trauma on affected couples (1). It is defined as the loss of two or more pregnancies before 24 weeks of gestation, although some guidelines may set the threshold at three losses (3, 4). The complexity of RPL arises from its multifactorial etiology, which includes anatomical, genetic, hormonal, immunological, and environmental factors (5, 6). Despite advancements in understanding and managing RPL, approximately 50% of cases remain unexplained (7, 8). This underscores the need for ongoing research and individualized treatment approaches to improve outcomes for affected couples.

The anti-paternal cytotoxic antibody (APCA) is produced by the mother against paternal antigens present in the fetus. Its presence has been hypothesized to play a role in pregnancy outcomes, particularly in recurrent miscarriage. The APCA test has become an important diagnostic tool for understanding recurrent miscarriages, especially in cases where no clear cause is identified. This test evaluates the presence of antibodies against paternal leukocytes, which may indicate an immunological response contributing to pregnancy loss (9). APCA testing is typically conducted after a woman has been immunized with paternal lymphocytes. A study involving 549 women found that 16.9% tested positive for APCA, among whom 52.7% achieved a successful pregnancy, suggesting a potential link between the presence of APCA and improved pregnancy outcomes (10). Another study involving 306 women indicated that the incidence of positive APCA tests was significantly higher in women who successfully completed pregnancies (32%) compared to those experiencing spontaneous abortions (10%) (3). Despite its diagnostic potential, the reliability of the APCA test is often questioned. Some evidence indicates that not all women experiencing miscarriages exhibit these antibodies, and their levels may vary between pregnancies (3). Additionally, only a small percentage of women with recurrent miscarriages show positive results for APCA (11). Research indicates that while APCA testing has been linked to various autoimmune conditions, its reliability as a diagnostic tool for RPL is questionable due to inconsistent results. The aim of this study was to systematically review existing literature on the diagnostic utility of APCA testing in women with recurrent miscarriage (RM), focusing on the prevalence, reliability, and predictive value of this test.

2- MATERIALS AND METHODS

An extensive investigation into the evidence concerning anti-paternal cytotoxic antibodies (APCA) and their relationship with recurrent miscarriage was conducted across various databases, including PubMed, Scopus, Web of Science, CIVILICA, and Google Scholar, up to March 2024. The search employed keywords and medical subject headings (MeSH) such as 'recurrent miscarriage,' 'anti-paternal cytotoxic antibody,' 'APCA,' 'reproductive immunology,' and 'recurrent pregnancy loss.'

The inclusion criteria for the studies were as follows: they had to be published in peer-reviewed journals, address the relationship between APCA and recurrent miscarriage (RM), consist of original research or reviews/meta-analyses, and be available in either English or Persian. The exclusion criteria included case reports or abstracts without full-text access, studies that did not specifically investigate APCA

in the context of RM, and those addressing other antibody types unrelated to APCA.

The search process was conducted independently by two reviewers with duplication; any disagreements were resolved by a supervisor. A narrative synthesis was performed to summarize findings from selected studies, emphasizing observed trends in APCA prevalence and diagnostic techniques used. Approval from a research ethics committee was not necessary since the study analyzed only publicly available articles. The research adhered to ethical standards by respecting copyright laws and ensuring transparency in its methods and sources.

3- RESULTS

The purpose of this overview was to review and integrate the available literature concerning the prevalence, diagnostic methods, and ramifications of anti-paternal cytotoxic antibodies (APCA) in women experiencing recurrent miscarriages.

3-1. Definition of recurrent miscarriage

Definitions of recurrent miscarriage (RM) can vary based on cultural and medical perspectives, highlighting the need for ongoing review and consensus within the medical community (5). This variability can complicate diagnosis and treatment protocols.

- **Two or more losses**: Some guidelines, particularly in Europe, define RM as two or more miscarriages (1).
- **Three or more losses**: The more common definition in clinical practice is three or more consecutive miscarriages, which aligns with guidelines from various medical authorities (3).

3-2. Causes of Recurrent Miscarriage

Causes of recurrent miscarriage include several factors that can be categorized into genetic, anatomical, endocrine, autoimmune, and thrombophilic issues:

3-2-1. Genetic Factors

- **Chromosomal Abnormalities**: Genetic factors are significant contributors to recurrent miscarriage, with chromosomal abnormalities in either parent accounting for approximately 50-80% of early pregnancy losses. These abnormalities may occur randomly during conception or can be inherited from one or both parents.

3-2-2. Anatomical Issues

- **Uterine Malformations**: Structural abnormalities such as a septate uterus, fibroids, or polyps can significantly contribute to pregnancy loss. These conditions can interfere with implantation or the maintenance of a viable pregnancy. Approximately 15% of women evaluated for recurrent miscarriage have identifiable anatomical defects.

3-2-3. Endocrine and Metabolic Disorders

- **Hormonal Imbalances**: Conditions like thyroid dysfunction (both hypo- and hyperthyroidism), and poorly controlled diabetes are associated with recurrent pregnancy loss (RPL). Proper management of these conditions is essential to reduce the risk of miscarriage.

3-2-4. Autoimmune Disorders

- **Antiphospholipid Syndrome:** This condition can increase the risk of recurrent miscarriage by causing blood clotting issues that affect placental function. It is present in about 15% of women experiencing recurrent miscarriages.

3-2-5. Thrombophilia

- **Inherited Blood Clotting Disorders**: Thrombophilia may also play a role in

RPL, particularly when it leads to placental insufficiency due to clot formation. This can complicate pregnancies and increase the likelihood of miscarriage (2, 3, 12).

Understanding these factors is crucial for addressing recurrent miscarriages effectively, as many women remain unexplained despite extensive testing.

3-3. Psychological impact and supporting couples

Recurrent miscarriage poses significant emotional and psychological challenges for couples, leading to profound grief, anxiety, and symptoms of depression that can persist long after the loss. The unique experiences of each partner necessitate a compassionate and comprehensive support system that addresses both their individual and shared emotional needs. By encouraging open dialogue, fostering mutual understanding, and engaging in professional counseling, couples can effectively navigate the challenges associated with their grief. Supportive care that validates their experiences and acknowledges their pain is essential for promoting healing and resilience. Ultimately, addressing the psychological impact of recurrent miscarriage not only facilitates individual recovery but also strengthens the couple's bond, enabling them to cope with their losses and move forward together. An individualized approach to support is vital for helping couples in their journey toward hope and recovery after experiencing multiple pregnancy losses (1, 2, 13).

3-4. Key Aspects of APCA Testing

3-4-1. Purpose: The objective of the APCA test is to evaluate specific immune responses that may hinder successful implantation and the continuation of pregnancy. This test is particularly relevant for women who have experienced recurrent miscarriages, as they often show a deficiency in protective antibodies, which can lead to fetal rejection (14).

3-4-2. Testing Process: Typically, the APCA testing process is conducted after a woman has been immunized with paternal lymphocytes. This testing assesses the maternal immune response to paternal antigens associated with sperm (15).

3-4-3. Diagnostic Criteria: Diagnosing Antiphospholipid Syndrome (APS) requires confirming the presence of antiphospholipid antibodies (aPL) on two separate occasions, with at least a 12-week interval between tests. This confirmation is crucial for evaluating the risk of recurrent pregnancy loss (RPL) (16).

3-4-4. Types of Antibodies: Among the various types of antibodies, lupus anticoagulant (LA) is particularly significant, as it interferes with coagulation processes, thereby increasing the likelihood of thrombotic events and potential complications during pregnancy (16, 17).

3-4-5. Risk Stratification: High-titer antiphospholipid antibodies (aPL), and the presence of multiple aPL are associated with an increased risk of thrombotic events and recurrent pregnancy loss. This underscores the importance of careful monitoring and management in these cases (18, 19).

3-4-6. Overview of APCA Testing: The APCA test measures specific immune responses that may inhibit successful implantation and maintenance of pregnancy. Women with recurrent miscarriages often show a lack of these protective antibodies, which can lead to fetal rejection (16). APCA testing is typically conducted after a woman has been immunized with paternal lymphocytes. A study involving 549 women found that 16.9% tested positive for APCA, among whom 52.7% achieved a successful pregnancy, suggesting a potential link between the presence of

APCA and improved pregnancy outcomes (17). Furthermore, research indicates that the incidence of positive APCA tests is significantly higher in women who successfully complete pregnancies (32%) compared to those experiencing spontaneous abortions (10%) (3). While the APCA test provides essential insights into the potential risks of recurrent pregnancy loss (RPL) for those who are aPL-positive, it does not address the complete range of factors affecting pregnancy outcomes. Genetic predispositions and environmental influences are critical in shaping these outcomes, highlighting the complexity of predicting RPL in affected individuals (20-23).

3-5. Diagnostic and Predictive Value

Anti-paternal cytotoxic antibodies (APCA) are a specific type of antibody that can be significant in various medical contexts, particularly in reproductive immunology and transplantation. Understanding their reliability and predictive value is crucial for their application in clinical settings.

3-5-1. Flow Cytometry Findings: Flow cytometry findings indicate that the presence of anti-paternal antibodies, particularly APCA, may correlate with improved pregnancy outcomes. This method is utilized to quantitatively evaluate the immune response to paternal antigens in maternal serum. Research suggests that APCA serves as an effective screening tool for diagnosing and forecasting outcomes in patients experiencing recurrent pregnancy loss. Notably, positive results from flow cytometry cross-match (FCXM) are associated with a significant correlation between the presence of these antibodies and successful pregnancies, highlighting APCA's potential utility as a prognostic marker in clinical settings (24, 25).

3-5-2. Cytotoxic T-Lymphocyte Precursor Frequencies: Elevated levels of cytotoxic T-lymphocytes have been detected in women experiencing unexplained recurrent miscarriages, suggesting a potential immunological factor. The presence of these lymphocytes indicates a modified immune response that may contribute to pregnancy loss (26).

3-5-3. Incidence in Pregnancies: A study involving 306 women found that the incidence of serum APCA was 32% in successful pregnancies, compared to only 10% in those that ended in spontaneous abortion. This suggests a correlation between the presence of APCA and successful pregnancy outcomes. However, the reliability of APCA as a consistent marker is questionable due to its transient nature, often disappearing between pregnancies (3, 25).

3-5-4. Predictive Value of APCA: The predictive capability of APCA is substantial. Studies indicate that women with recurrent miscarriages who test positive for APCA show an increase in live birth rates from 18.5% to 53.7%. This marked improvement highlights the potential of this antibody as a predictor of pregnancy success (11). However, it is essential to consider that factors such as maternal age, medical history, and genetic background can influence both the production of APCA and the overall likelihood of achieving a successful pregnancy (27, 28).

3-6. Impact of APCA on Pregnancy Outcomes

The investigation into the role of APCA in pregnancy outcomes has yielded mixed results, reflecting the complexity of immunological interactions during gestation. While some studies suggest a potential benefit of these antibodies, others indicate no significant impact on pregnancy success.

3-6-1. Varied Results: A systematic review revealed no significant association

between HLA class I or II antibodies and pregnancy outcomes, underscoring the variability in findings attributed to differing methodologies employed in various studies (10).

3-6-2. Recurrent Miscarriages: In cases of recurrent spontaneous abortion (RSA), women exhibited an increase in specific anti-paternal cytotoxic T-cells following immunization, indicating a likelihood of sensitization rather than a protective response (26).

3-6-3. Live Birth Rates: Research indicates that women with positive APCA tests experience significantly higher live birth rates post-immunization, with some studies reporting increases from 18.5% to 53.7% in specific cohorts following treatment (11). This improvement highlights the potential effectiveness of immunotherapy targeting these antibodies.

While APCA testing shows promise, some experts caution against over-reliance on these antibodies, as they are not universally present in all women with recurrent miscarriages, and their absence does not definitively indicate a lack of immunological issues (3).

3-7. Limitations of APCA Testing

Relying solely on anti-paternal cytotoxic antibody testing for diagnosing recurrent miscarriage has notable limitations, as it does not provide a comprehensive understanding of the multifactorial nature of recurrent pregnancy loss. The following are the key limitations associated with APCA testing:

3-7-1. Low positive rate: Findings from APCA testing reveal a low positive rate, with only 16.9% of the women tested being positive for APCA. Among those who were positive, a successful pregnancy was achieved in just 52.7% of cases (29).

3-7-2. Inadequate correlation with clinical outcomes: Research indicates that while positive APCA tests are more common in successful pregnancies, their absence does not necessarily correlate with miscarriage outcomes. A lower incidence of positive APCA tests was observed in pregnancies that ended in spontaneous abortion compared to those that were successful (3, 30, 31). This suggests that APCA may not be a definitive predictor of pregnancy viability.

3-7-3. Presence of antibodies: Many women experiencing unexplained recurrent miscarriages do not exhibit APCA, indicating that the presence of these antibodies is not a definitive marker for predicting pregnancy success (3, 30, 31).

3-7-4. Neglect of significant causes: APCA testing fails to consider other critical factors contributing to recurrent miscarriage, such as anatomical abnormalities, hormonal imbalances, and genetic issues. Comprehensive evaluations should include assessments for thrombophilia and uterine anomalies to effectively identify underlying causes (3, 14, 30).

3-7-5. Unproven efficacy: The effectiveness of immunotherapy based on APCA results remains under scrutiny. Some studies suggest that such treatments may do more harm than good, raising concerns about their safety and efficacy in managing recurrent miscarriages. Conversely, certain researchers argue that APCA testing may still hold significance in specific situations, especially when used alongside other diagnostic tools (31).

3-7-6. Lack of standardization: There is no universally accepted protocol for conducting APCA tests, leading to inconsistencies in results. This lack of standardization complicates the interpretation of findings and their applicability to clinical practice (3, 32).

3-7-7. Transient nature: The transient characteristics of APCA mean it may not be detected during critical phases of

pregnancy, thus limiting its applicability for ongoing monitoring or diagnostic evaluation (3).

3-7-8. Potential for misdiagnosis: Relying on self-reported data regarding pregnancy losses can lead to inaccuracies, as only a limited number of these losses are verifiable through clinical records. This further complicates the assessment of recurrent pregnancy loss (33).

3-7-9. Inconsistent results: Studies have highlighted variability in the rates of APCA positivity among different demographic groups, raising concerns about its reliability as a diagnostic tool. For instance, APCA is often undetectable before 28 weeks of gestation and tends to disappear between pregnancies, complicating its role as a consistent marker for recurrent pregnancy loss (3, 33).

3-7-10. Variable incidence and timing: The incidence of APCA varies significantly depending on gestational age. Positive APCA tests are rare before 28 weeks of gestation, raising questions about their utility as a diagnostic tool in early pregnancy loss. In cohort studies, the incidence of APCA was found to be 32% in successful pregnancies compared to only 10% in those ending in spontaneous abortion (3).

3-7-11. Limited understanding of mechanisms: The mechanisms by which APCA may influence pregnancy outcomes are not fully understood. Evidence suggests that reduced or absent APCA production in women with recurrent spontaneous abortion may stem from an inability of paternal spermatozoa to induce antibody production, indicating a complex interplay between immune response and reproductive biology that is not captured by APCA testing alone (33).

3-7-12. Psychological impact: The reliance on APCA testing may have psychological implications for couples experiencing recurrent miscarriages. Misinterpretation of test results or failure to identify a cause can lead to increased anxiety and distress without appropriate support or interventions (32).

3-8. Alternative Predictive Models

In recent years, the understanding of miscarriage risk has evolved significantly, leading to the development of various predictive models aimed at improving outcomes for women experiencing recurrent pregnancy loss. Traditional methods, such as the APCA test, have provided some insights into individual risk factors; however, their predictive accuracy can be variable. This has prompted researchers to explore more comprehensive approaches that incorporate a wider array of immunological and genetic factors. By evaluating emerging risk scoring systems and routine pre-pregnancy tests, we can gain valuable insights into their effectiveness in predicting miscarriage risk and ultimately enhancing clinical decision-making for at-risk women. The following results highlight the advancements in predictive modeling and their implications for improving treatment outcomes:

3-8-1. Risk Scoring Systems: Emerging predictive models that consider multiple risk factors, including antinuclear antibodies and protein S deficiency, have demonstrated a higher level of accuracy in forecasting pregnancy loss compared to the APCA used independently (34). Recent analyses indicate that these comprehensive risk assessment tools could enhance the accuracy of predictions for women at risk of miscarriage.

3-8-2. Routine Pre-Pregnancy Tests: Studies have also highlighted the effectiveness of routine pre-pregnancy tests in establishing risk prediction models. These models reportedly achieve predictive accuracies of around 74.53%, suggesting that other biomarkers may be more reliable than APCA for assessing

miscarriage risk (35). This underscores the importance of conducting broader assessments that incorporate diverse immunological and genetic factors, rather than solely focusing on APCA levels.

Although the APCA test may provide some benefits in identifying specific risks associated with recurrent miscarriage, its variable predictive accuracy emphasizes the need for more comprehensive risk assessment models. Such models should encompass a wider range of factors to improve treatment outcomes for women experiencing recurrent pregnancy loss.

3-9. Guidelines and Recommendations

3-9-1. Importance of Testing for APCA: Professional guidelines emphasize the necessity of testing for antiphospholipid antibodies (aPLs) in women who have experienced recurrent miscarriages, particularly after ruling out other potential causes. This testing is particularly relevant for cases of unexplained pregnancy losses occurring before ten weeks of gestation or following a single loss at or beyond this gestational period (32, 36).

3-9-2. Treatment Strategies: The Royal College of Obstetricians and Gynaecologists (RCOG) recommends using low-dose aspirin in combination with heparin as a treatment strategy. This recommendation is supported by clinical trial findings that highlight the importance of early detection through tests such as antiphospholipid antibody tests (37, 38). The combination therapy has been shown to significantly increase the rate of live births in women with a history of recurrent miscarriage associated with antiphospholipid antibodies compared to aspirin alone. Specifically, the live birth rate with the combination treatment is approximately 71%, compared to 42% for those using aspirin alone. This underscores the efficacy of the combination approach in improving pregnancy outcomes within this patient population (39, 40).

3-10. Considerations and Cautions

While the assessment of APCA yields significant insights into the immunological components related to recurrent miscarriages, it is imperative to consider the findings judiciously. The inconsistent occurrence of APCA in affected individuals reveals the multifaceted nature of recurrent pregnancy loss, indicating that exclusive reliance on this test could lead to incomplete or misleading outcomes. A comprehensive assessment that includes a range of diagnostic methods—such as genetic, hormonal, and anatomical evaluations—is essential for understanding the complex nature of recurrent miscarriages. Additionally, while some women may find immunotherapy beneficial based on APCA findings, treatment must be tailored to the individual and consider a wider array of health factors. Continuous research is crucial for enhancing our understanding of APCA function and for developing improved strategies to manage recurrent miscarriages. This ensures that women receive the most effective and well-informed care available (3, 14, 28, 33, 41, 42). Although APCA testing has shown promise as a valuable tool in the understanding and management of recurrent miscarriage, further research and careful clinical application are necessary to fully harness its diagnostic and prognostic potential.

4- CONCLUSION

In summary, while the presence of anti-paternal cytotoxic antibodies (APCA) offers valuable insights into the immune-related factors contributing to recurrent pregnancy loss (RPL), it is essential to recognize that it is not a definitive predictor of pregnancy outcomes. The interplay of genetic, environmental, and immunological factors necessitates a comprehensive and personalized approach to treatment. Continued research is crucial

to further validate the role of APCA testing and to refine strategies for managing RPL effectively. By enhancing our understanding of these complex interactions, we can improve care for women facing the emotional and physical challenges of recurrent miscarriage, ultimately fostering better reproductive outcomes. This conclusion reinforces the complexity of RPL while highlighting the need for tailored approaches and further investigation.

5- CONFLICT OF INTEREST: None.

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