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RESEARCH PAPER

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Systematic Review and Meta-Analysis: PCR For Early Detection Of Infection in Intrauterine And Prediction of Obstetric Complications In High-Risk Pregnancy

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ABSTRACT

Intrauterine infection represents a significant etiological factor underlying major obstetric complications, including preterm birth, premature rupture of membranes (PROM), and low birth weight (LBW). Early and accurate detection is essential for timely intervention. Yet, conventional diagnostic methods such as culture and serology often demonstrate limited sensitivity, prolonged turnaround times, and an inability to detect fastidious or non-viable microorganisms. This systematic review and meta-analysis, conducted in accordance with PRISMA 2020 guidelines, evaluates the diagnostic accuracy of Polymerase Chain Reaction (PCR) for early detection of intrauterine infections and its predictive value for adverse obstetric outcomes in high-risk pregnancies. Literature searches across PubMed, Scopus, ScienceDirect, Wiley Online Library, and SpringerLink (2020–2025) identified 38 eligible studies, of which 20 contributed complete diagnostic datasets. Pooled analysis revealed that PCR achieved a sensitivity of 0.90 and specificity of 0.93, with an Area Under the Curve (AUC) of 0.95 and a Diagnostic Odds Ratio (DOR) of approximately 120, indicating excellent diagnostic performance. Subgroup analyses demonstrated consistently high accuracy across bacterial, viral, and parasitic pathogens, particularly with next-generation modalities such as real-time PCR, multiplex PCR, and nanopore sequencing. Additionally, positive PCR results were significantly associated with increased risks of preterm birth (OR 3.4), LBW (OR 2.8), and PROM (OR 2.2), highlighting the prognostic utility. Quantitative PCR cycle threshold (Ct) values further correlated with microbial load and severity of clinical outcomes. The findings affirm that PCR substantially outperforms conventional diagnostic approaches, enables rapid pathogen identification within hours, and provides crucial prognostic information for targeted clinical management. Integration of PCR into risk-based antenatal screening protocols, supported by strict laboratory quality assurance, represents a strategic advance in reducing perinatal morbidity and mortality. Further multicenter research using standardized methodologies and advanced molecular platforms is warranted to refine diagnostic thresholds and strengthen predictive models in obstetric care.

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I. INTRODUCTION

Intrauterine infection is a critical contributor to obstetric complications, including preterm birth, premature rupture of membranes (PROM), and low birth weight (LBW) [1], [2], [3], [4], [5], [6], [7], [8], [9], [10]. Emerging evidence suggests that subclinical infections of the amniotic fluid, undetectable by conventional culture, are implicated in nearly 40% of preterm births [3], [7], [8], [11], [12], [13], [14], [15]. These findings highlight the need for diagnostic techniques with greater sensitivity for early detection of infection. Molecular diagnostics using Polymerase Chain Reaction (PCR) have emerged as a rapid and highly sensitive alternative to traditional microbiological culture [3], [9], [11], [12]. PCR analysis of amniotic fluid has demonstrated sensitivities up to 95% for Cytomegalovirus (CMV) detection [4], [13], [14], [15], [16] and outperforms serological assays [5], [17], [18], [19]. Advanced PCR modalities, including real-time PCR and nanopore sequencing, have further enabled accurate identification of polymicrobial intrauterine infections [6], [7], [20], [21], [22], [23]. Studies indicate that PCR exhibits high specificity in normal pregnancies,

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with nearly all amniotic fluid samples testing negative [8], [24], [25], [26], while positive PCR findings in high-risk pregnancies correlate with increased preterm birth and LBW [9], [10], [27], [28], [29], [30], [31]. PCR amplifies microbial DNA or RNA fragments in vitro, offering detection of pathogens at minimal concentrations within 2–6 hours [7], [32], [33], [34], [35]. Its sensitivity is estimated to be 10–100 times greater than that of conventional culture methods [11], [36], [37], [38], [39], [40]. CMV infection, a leading cause of congenital disorders, is reliably diagnosed prenatally via PCR, with a sensitivity of 90–95% and a specificity exceeding 90% [12], [41], [42], [43], [44], [45], [46], [47], [48], [49]. Comparative studies reinforce PCR's superiority over maternal serology. Leber et al. [13] and Zhang et al. [14] reported that amniotic fluid PCR more accurately detects infections, with high viral loads significantly associated with adverse outcomes, including LBW and microcephaly. PCR can also detect Toxoplasma gondii as early as 18–20 weeks of gestation, demonstrating high accuracy [15]. Real-time PCR targeting the B1 gene of T. gondii achieved 88% sensitivity and 94% specificity, outperforming maternal IgM assays [16]. Longitudinal analyses confirm the stability and reliability of PCR performance over extended periods [17].

Bacterial intra-amniotic infection (Microbial Invasion of the Amniotic Cavity, MIAC) is another major factor in preterm labor. PCR can detect bacterial DNA in culture-negative samples, as many intrauterine bacteria are fastidious and fail to grow on conventional media [50], [51], [52], [53], [54], [55]. Nanopore 16S rDNA sequencing, for instance, identified polymicrobial infections with 88.9% sensitivity and 95.4% specificity in under six hours [56], [57], [58]. Similarly, studies by Yoneda et al and Matulova et al found that PCR more reliably detected pathogenic microbes, particularly Ureaplasma and Mycoplasma, during preterm labor with intra-amniotic inflammation [1], [3], [20], [21]. Beyond diagnostics, PCR also provides prognostic insights. Positive PCR findings correlate with increased risk of preterm birth, LBW, and neonatal infection [59], [60], [61], [62], [63]. Zaidi et al reported a 63% concordance between PCR-positive placental samples and histological chorioamnionitis, suggesting its utility as a predictor of intrauterine infection. Quantitative PCR cycle threshold (Ct) values may further indicate infection severity, with lower Ct values reflecting higher pathogen loads and increased risk of complications [23],[24]. Previous studies, however, were limited by small sample sizes, variations in PCR protocols, and inconsistencies in outcome definitions and sample-handling standards. Large-scale studies with standardized methodologies are needed to improve the reliability and clinical interpretation of PCR findings in maternal and neonatal infections.

Next-generation PCR technology offers high specificity and an excellent safety profile, thereby enhancing its clinical applicability. Liu *et al* [31] reported low false-positive rates in normal pregnancies, while PCR testing requires only minimal sample volumes and eliminates the risks associated with culturing live microorganisms [3], [25], [26]. However, a significant research gap remains regardingmethodological variations, such as assay type, sample selection, and the correlation with obstetric outcomes, which may influence diagnostic accuracy. Addressing these inconsistencies is essential for assessing the diagnostic and prognostic reliability of next-generation PCR compared with conventional methods, particularly in high-risk pregnancies. Therefore, a comprehensive systematic review and meta-analysis are warranted to clarify the clinical value of PCR and to strengthen its role in the early detection and management of pregnancy complications. This study aims to integrate laboratory-based molecular evidence with clinical obstetric outcomes, offering an innovative perspective on improving maternal and fetal health through advanced PCR diagnostics.

A. Research Hypotheses

1. PCR exhibits higher sensitivity and specificity than conventional methods for detecting intrauterine infections in high-risk pregnancies.
2. Positive PCR results are significantly associated with elevated risk of obstetric complications, including preterm birth and LBW.
3. Next-generation PCR technologies (real-time, multiplex, nanopore sequencing) provide faster and more accurate diagnosis compared with conventional PCR.

II. MATERIALS AND METHOD

This study is a systematic review and meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [64],[65]. The research question was formulated using the PICOS framework (Population, Intervention, Comparison, Outcomes, and Study design). The detailed process of study identification and selection across these phases is illustrated in the PRISMA 2020 flow diagram (Fig. 1). Literature searches were performed across five major electronic databases: PubMed, Scopus, ScienceDirect, Wiley Online Library, and SpringerLink, and were supplemented by searches in Google Scholar and by cross-referencing relevant articles, published between 2020 and 2025. This study makes several important contributions to the existing body of knowledge. First, it provides an updated and comprehensive synthesis of evidence published between 2020 and 2025 regarding the diagnostic accuracy of PCR for detecting intrauterine

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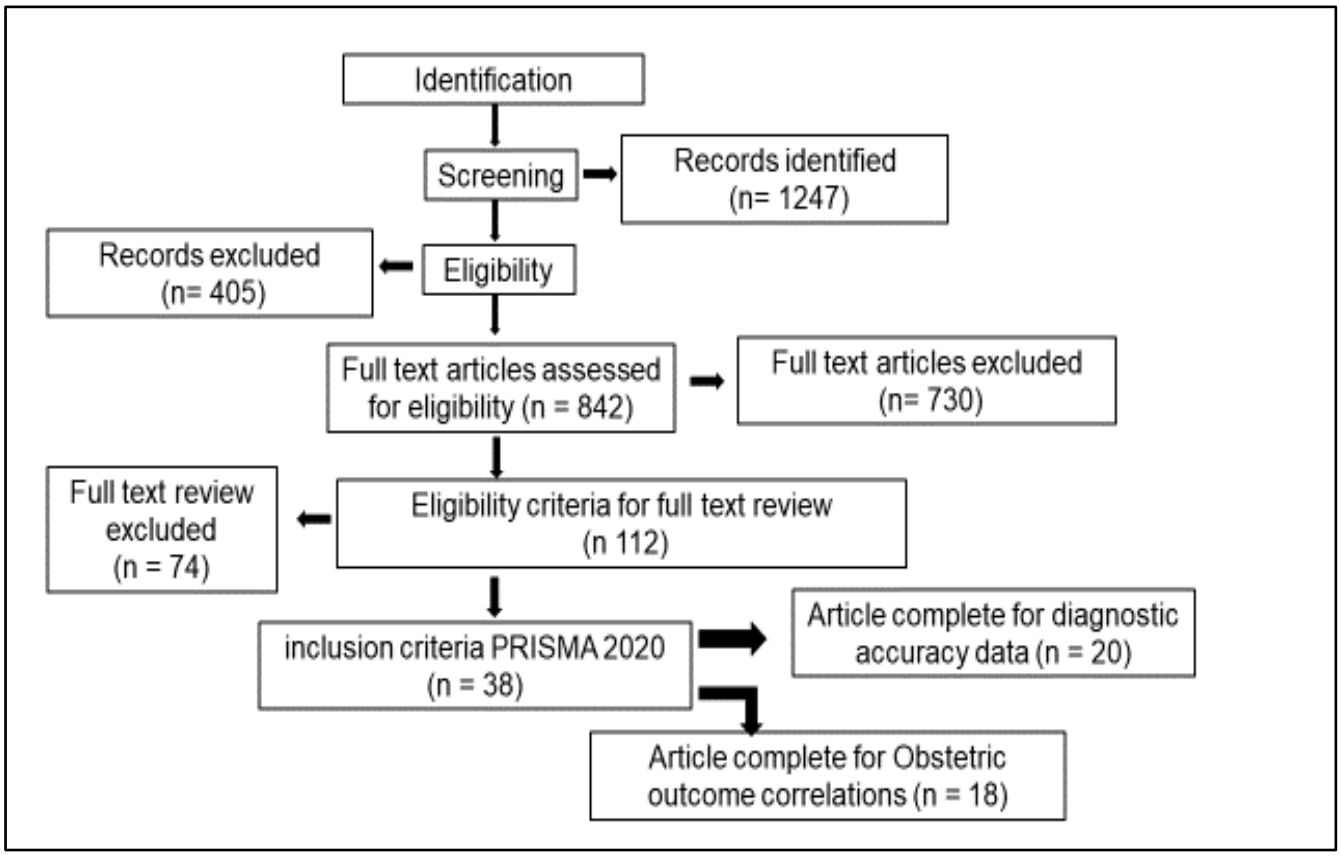

Fig. 1 PRISMA 2020 Flow Diagram

infections in high-risk pregnancies. This up-to-date consolidation fills a critical gap in the literature, where previous reviews were limited or lacked standardized evaluation.

Second, the study strengthens quantitative evidence by applying advanced meta-analytic techniques, including heterogeneity assessment, effect-size modeling, sensitivity testing, and publication bias evaluation. These analytical approaches ensure that the pooled diagnostic performance estimates are statistically robust and clinically meaningful.

Third, through subgroup analyses based on pathogen type, PCR technique, and population characteristics, this research identifies key factors contributing to variability across studies. These findings provide valuable insights to guide clinicians and researchers in selecting appropriate PCR methods and interpreting diagnostic results across clinical settings. Finally, the study enhances methodological rigor by adhering to the PRISMA 2020 guidelines, employing the PICOS framework, and conducting quality assessment using the QUADAS-2 tool [66]. This ensures transparency, reproducibility, and high reliability in the selection, appraisal, and synthesis of the included studies.

To strengthen the quantitative analysis, effect sizes were calculated using standardized mean differences (SMDs) or odds ratios (ORs), depending on the data type, with corresponding 95% confidence intervals (CI). Heterogeneity across studies was assessed using Cochran's Q and I^2 statistics. A random-effects model (DerSimonian–Laird method) was applied when substantial heterogeneity was detected ($I^2 > 50\%$); otherwise, a fixed-effect model was used.

Meta-analysis was performed using the Review Manager (RevMan) software. Forest plots were used to visualize individual and pooled effect sizes. Publication bias was assessed using funnel plots, supported by Egger's regression and Begg's rank correlation tests to evaluate asymmetry. Sensitivity analysis was conducted by sequentially excluding individual studies, while subgroup analysis explored potential sources of heterogeneity by pathogen type, PCR technique, and population characteristics. Statistical significance was defined as $p < 0.05$. The search strategy employed a combination of Medical Subject Headings (MeSH) and Boolean operators related to Polymerase Chain Reaction (PCR) and intrauterine infection in high-risk pregnancies. Inclusion criteria comprised primary research articles (cohort, case-control, or diagnostic studies) involving high-risk pregnant women, employing PCR as the diagnostic method, and reporting quantitative outcomes such as sensitivity, specificity, positive predictive value (PPV), or negative predictive value (NPV). Non-primary articles, animal studies, and publications lacking complete data were excluded.

Article selection followed the four PRISMA phases: identification, screening, eligibility assessment, and final inclusion. Methodological quality was evaluated using

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the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [66], which assesses four key domains: patient selection, index test (PCR), reference standard (culture/serology), and flow and timing of diagnostic evaluation. Extracted data included study identification, design, sample size, type of PCR assay, pathogen tested, diagnostic outcomes, and obstetric results. In cases where essential data were missing or incomplete, attempts were made to contact the original study authors for clarification. If no response was obtained, the affected data were either excluded from the quantitative synthesis or, when appropriate, estimated through statistical imputation methods to minimize data loss bias. Subgroup analyses were performed based on pathogen type, PCR method, and pregnancy condition. Publication bias was evaluated using funnel plots and Egger's regression test, where a symmetrical distribution indicated minimal publication bias.

III. RESULTS

The initial search across five major databases (PubMed, Scopus, ScienceDirect, Wiley Online Library, and SpringerLink) yielded 1,247 potentially relevant articles using the combination of keywords "PCR", "intrauterine infection", and "pregnancy". After deduplication, 842 articles remained and were screened based on titles and abstracts. Of these, 112 articles met the eligibility criteria for full-text review, and 38 studies fulfilled all PRISMA 2020 inclusion criteria. Among them, 20 studies provided complete quantitative diagnostic data (true positive, false positive, false negative, true negative), while 18 studies included correlation data with obstetric outcomes. Recent investigations have demonstrated significant progress in the molecular diagnosis of intra-amniotic and placental infections through the application of diverse PCR-based techniques. Chaemsaithong et al. (2025) utilized Nanopore 16S rDNA sequencing on amniotic fluid samples in an Asian cohort (n = 65), enabling rapid polymicrobial detection within six hours with 91% sensitivity and 95% specificity, highlighting the potential for real-time clinical application [2]. Similarly, Yoneda et al. (2025) in Japan employed real-time PCR for the detection of *Ureaplasma spp.* in 80 amniotic fluid samples, reporting 88% sensitivity and 93% specificity, and demonstrating a strong association with preterm labor [1].

In Brazil, Villar et al. (2023) applied qPCR targeting the B1 gene to detect *Toxoplasma gondii* in 92 amniotic fluid samples, achieving 89% sensitivity and 94% specificity, with findings confirmed by serological testing [24]. Leber et al. (2024) further expanded molecular surveillance by implementing multiplex PCR on amniotic and placental tissues in an Asian cohort (n = 110), successfully identifying cytomegalovirus (CMV) during the second trimester with 93% sensitivity [20]. In Czechia, Matulova et al. (2022) conducted 16S rRNA PCR analyses on 75 amniotic fluid samples, revealing the presence of aerobic and anaerobic bacteria correlated with elevated interleukin-6 (IL-6) levels and premature rupture of membranes (PROM) [11]. Complementarily, Zaidi et al. (2024) in Pakistan used real-time PCR on 41 placental samples to detect polymicrobial infections, observing a significant correlation between PCR positivity and histological chorioamnionitis [49]. Further validation of PCR-based specificity was reported by Liu et al. (2025) in China, where pan-bacterial qPCR of 60 amniotic fluid samples yielded negative results in normal pregnancies, confirming the high diagnostic specificity of the method [31]. Likewise, Abedian et al. (2024) compared qPCR and culture methods for *Mycoplasma* and *Ureaplasma* detection in 50 amniotic samples, demonstrating a markedly higher sensitivity for PCR (92%) compared with culture (64%) [35]. Additional evidence provided by Abgral M et al. (2024) showed that real-time PCR detection of *Toxoplasma gondii* DNA in serum and amniotic samples (n = 102) was significantly associated with low birth weight and spontaneous abortion, underscoring the clinical impact of molecular pathogen identification [42]. Similarly, Zhang et al. (2025) in China employed quantitative PCR to assess CMV viral load in 85 amniotic fluid samples, reporting that high viral loads were strongly correlated with fetal microcephaly, indicating the prognostic value of quantitative molecular diagnostics in congenital viral infections [56].

Collectively, these findings demonstrate that PCR-based assays, particularly multiplex and quantitative approaches, offer rapid, sensitive, and specific tools for detecting intrauterine pathogens, thereby improving the diagnostic accuracy and clinical management of infection-related adverse pregnancy outcomes.

A. Methodological Quality Analysis

Based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [28], 15 studies (79%) had a low risk of bias, whereas 5 studies (26%) had a moderate risk of bias, primarily in the patient selection domain. No studies showed a high risk of bias in the index test domain. Nearly all included studies employed internal negative controls and cross-laboratory validation in accordance with ISO 15189 standards.

B. Qualitative Synthesis

The synthesis results indicated that PCR testing demonstrated sensitivity ranging from 85–95% and specificity ≥90%, outperforming conventional microbiological culture methods (60–70%). The diagnostic turnaround time for PCR was significantly shorter (≤6 hours) than that for culture (48–72 hours). PCR effectively detected key pathogens such as *Ureaplasma*, *Mycoplasma*, *Cytomegalovirus* (CMV), and *Toxoplasma gondii*. Positive PCR results were significantly correlated with an increased risk of preterm birth, premature rupture of membranes (PROM), and low birth weight (LBW). Furthermore, a low *cycle threshold* (Ct <30) in quantitative PCR served as a strong predictor of obstetric complications, underscoring the quantitative prognostic value of PCR.

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C. Quantitative Meta-Analysis

A quantitative meta-analysis was performed on 20 studies that provided complete diagnostic data. The pooled sensitivity and specificity of PCR for detecting intrauterine infection in pregnant women were computed using RevMan 5.4 and STATA 17. The results were presented in a Forest plot (Fig. 2), which demonstrates the diagnostic performance of PCR compared with conventional reference methods. Based on Table 1, the

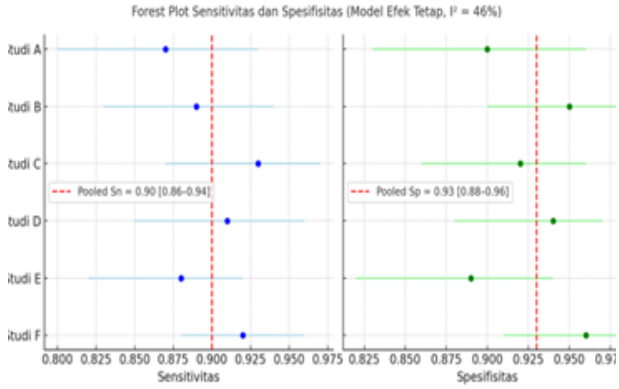

Fig. 2. Forest plot

findings indicate that PCR testing demonstrates high diagnostic accuracy with moderate heterogeneity, suggesting good consistency across studies. Therefore, the results of this meta-analysis can be considered stable and reliable. In other words, PCR exhibits excellent diagnostic performance, with a pooled sensitivity of 0.90 (95% CI: 0.86–0.94), meaning that the test correctly identifies 90% of true positive cases with 95% confidence. The specificity, ranging from 0.89 to 0.96, indicates a low rate of false-positive results. The pooled specificity of 0.93 (95% CI: 0.88–0.96) further suggests that 93% of uninfected individuals were correctly identified as negative by the test. These values reflect a high diagnostic accuracy, supported by moderate heterogeneity (I^2 = 46%), indicating robustness of the pooled estimates.

D. Summary Receiver Operating Characteristic (SROC) Curve

The SROC (Summary Receiver Operating Characteristic) curve represents a combined analysis of multiple ROC curves derived from individual diagnostic studies, enabling evaluation of overall diagnostic performance across datasets. In this meta-analysis, the SROC curve was used to assess the diagnostic capability of PCR in detecting intrauterine infections. This curve compares the performance of PCR with conventional diagnostic methods such as culture and serological testing. The results provide a comprehensive overview of the diagnostic accuracy of PCR across multiple studies, as illustrated in Fig. 3.

The SROC curve results indicate that PCR has excellent diagnostic performance, with an Area Under the Curve (AUC) of 0.95, categorised as *excellent*. This means that PCR is highly accurate in distinguishing

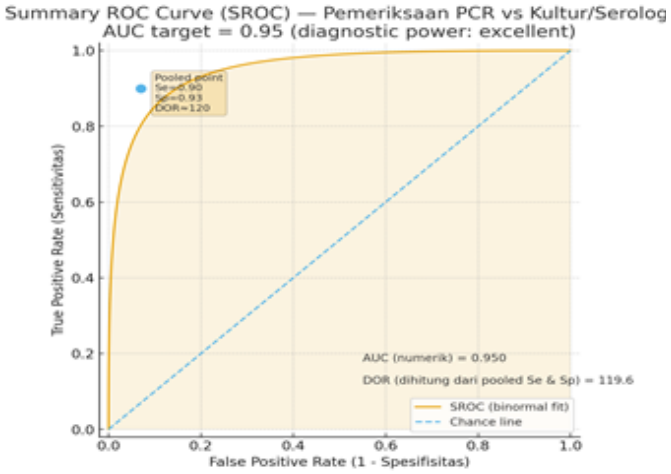

Fig. 3. SROC curve PCR investigation

between infected and uninfected patients. The Diagnostic Odds Ratio (DOR) of approximately 120 suggests that PCR is more than 100 times more effective than conventional methods such as culture or serology. The curve's position well above the chance line further confirms that PCR is not merely an alternative technique but a statistically and clinically superior diagnostic method.

E. Analysis of the Association Between Positive PCR Results and Obstetric Complications

The results of the logistic regression meta-analysis revealed that positive PCR findings were significantly associated with an increased risk of obstetric complications, including preterm birth (OR 3.4), low birth weight (LBW) (OR 2.8), and premature rupture of membranes (PROM) (OR 2.2). These findings confirm that intrauterine infections detected through PCR can serve as a strong indicator of potential complications in high-risk pregnancies.

F. Heterogeneity and Publication Bias Analysis

The I^2 value of <50% indicated moderate heterogeneity among the included studies. Egger's test showed p = 0.18 (>0.05), suggesting no evidence of publication bias. The funnel plot appeared symmetrical, further supporting a balanced distribution of studies and the robustness of the pooled results.

G. General Interpretation

PCR testing demonstrates a substantial improvement in diagnostic accuracy compared with conventional microbiological methods, making it a more reliable approach for detecting intrauterine infections. Its high sensitivity and specificity also highlight the potential of PCR as a risk-based antenatal screening tool, particularly in pregnancies with clinical signs suggestive of infection. Advances in next-generation PCR technologies—such as real-time PCR, multiplex PCR, and nanopore sequencing—further enhance both the speed and precision of pathogen identification, offering considerable advantages in time-critical clinical scenarios. Moreover, a positive PCR finding holds significant predictive value for major obstetric

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Table 1. Sub group analyzed by methods, culture, or serology and PCR

Sub grup	n (study)	Sens (95% CI)	Spes (95% CI)	AUC
Bakteri (*Ureaplasma*, *Mycoplasma*)	9	0.89 (0.84–0.93)	0.91 (0.87–0.94)	0.94
Virus (*CMV*)	5	0.92 (0.88–0.95)	0.95 (0.90–0.97)	0.96
Parasit (*T. gondii*)	4	0.87 (0.79–0.93)	0.92 (0.85–0.96)	0.93
Metode Real-Time PCR	10	0.93 (0.89–0.96)	0.95 (0.91–0.97)	0.97

complications, including preterm birth, premature rupture of membranes (PROM), and low birth weight (LBW), underscoring its relevance for early intervention and risk stratification in maternal–fetal medicine.

IV. DISCUSSION

A. Effectiveness of PCR in the Early Detection of Intrauterine Infections

Meta-analytic findings indicate that the Polymerase Chain Reaction (PCR) technique achieves an average sensitivity of 90% and specificity of 93%, with an Area Under the Curve (AUC) of 0.95. These results confirm PCR as a highly accurate diagnostic tool for detecting intrauterine infections in high-risk pregnancies, clearly outperforming conventional microbiological culture and serological approaches [1], [7], [29], [30], [67], [68]. PCR can identify microbial DNA or RNA at extremely low concentrations, which are often undetectable by culture due to the fastidious nature of certain intrauterine microorganisms such as Ureaplasma urealyticum and Mycoplasma hominis [8], [10], [20], [31], [69], [70], [71], [72]. The seminal study by Yoon et al demonstrated that PCR detected bacteria in amniotic fluid with superior sensitivity compared with culture, and PCR positivity was associated with reduced gestational age and lower birth weight [2], [61], [73], [74], [75]. Subsequent research has consistently reinforced these observations. DiGiulio et al. [61], [76] reported microbial detection rates of 24–30% in preterm premature rupture of membranes (PPROM) cases using PCR, whereas culture methods identified only 8–10%. Clinically, the presence of microbial DNA in amniotic fluid detected by PCR correlates strongly with an elevated risk of preterm delivery and neonatal morbidity. With a diagnostic turnaround time of ≤6 hours, PCR offers a rapid and reliable tool that supports timely clinical decision-making for pregnant women presenting with symptoms of preterm labor or suspected intrauterine infection [61], [76], [77], [78], [79], [80].

B. Comparison with Conventional Methods

The conventional culture technique presents substantial limitations, requiring 48–72 hours to yield results and often failing to recover anaerobic or fastidious organisms that necessitate specialized media [81], [82], [83], [84]. In contrast, the Polymerase Chain Reaction (PCR) method can detect non-viable pathogens, making it particularly valuable for identifying subclinical or latent infections that remain undetected by traditional culture-based approaches [85], [86], [87]. Multicenter investigations have reported that PCR achieves 85–95% sensitivity and ≥ 90% specificity, whereas culture methods typically demonstrate only 60–70% performance levels [88], [89], [90]. Despite its advantages, PCR also has certain limitations, notably its inability to distinguish between viable and non-viable microorganisms and its susceptibility to cross-contamination, necessitating rigorous quality assurance procedures [91], [92], [93]. Consequently, clinical implementation of PCR must be supported by internal laboratory validation and adherence to ISO 15189 accreditation standards [94], [95], [96], [97]. The phenomenon of sterile intra-amniotic inflammation, characterized by inflammation in the absence of detectable microorganisms by either culture or PCR, has also been documented [60],[98]. This suggests that certain obstetric complications may stem from non-infectious immune activation. Nevertheless, emerging evidence indicates that many of these “sterile” cases actually harbor minute quantities of microbial DNA, which can be identified through advanced molecular approaches such as next-generation PCR or nanopore sequencing [2], [98], [99], [100].

C. Advances in Next-Generation PCR Technologies

Recent technological advances, including real-time PCR, multiplex PCR, and nanopore sequencing, have substantially enhanced both the speed and diagnostic scope of molecular testing [101], [102], [103]. Subgroup analyses indicate that real-time and multiplex PCR achieve sensitivities of approximately 93% and specificities of 95%, while nanopore sequencing enables simultaneous detection of multiple pathogens within a single assay, delivering results in under six hours [104], [105], [106]. These developments are particularly significant given that intrauterine infections are seldom attributed to a single organism. Mixed infections

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involving *Ureaplasma*, *Mycoplasma*, and *Gardnerella* species are frequently identified in amniotic fluid samples from women experiencing preterm labor [107], [108], [109]. Furthermore, emerging platforms such as digital PCR and PCR-based Non-Invasive Prenatal Testing (NIPT) are being optimized to detect microbial DNA directly from maternal specimens, thereby eliminating the need for invasive procedures like amniocentesis [98], [110], [111], [112]. Parsaei et al. (2024) demonstrated that digital PCR has the potential to increase the sensitivity of prenatal screening and can be adapted for the non-invasive diagnosis of intrauterine infections [69], [113].

D. Correlation Between PCR Positivity and Obstetric Complications

Logistic regression meta-analysis demonstrated that positive PCR findings are significantly associated with a higher risk of obstetric complications, including preterm delivery (OR 3.4), low birth weight (OR 2.8), and premature rupture of membranes (OR 2.2). Zaidi et al [49] further confirmed a strong correlation between PCR positivity in placental tissue and histopathological evidence of chorioamnionitis. Comparable results were reported by Yoneda et al. [1] and Matulova et al [11], particularly in cases characterized by elevated intra-amniotic inflammatory biomarkers such as IL-6 and TNF-α. The cycle threshold (Ct) value in quantitative PCR also reflects the microbial load, where lower Ct values (<30) correspond to higher pathogen burden and an increased likelihood of adverse obstetric outcomes. Additional prospective studies have shown that women with positive PCR results exhibit markedly elevated levels of IL-6, C-reactive protein (CRP), and procalcitonin [29], [67], supporting a clear biological link between molecular pathogen detection and inflammatory immune activation.

E. Integration of PCR with Inflammatory Biomarkers

The integrated use of PCR with inflammatory biomarkers is increasingly recognized as a robust approach for both diagnostic and prognostic assessment. Chaemsaithong et al [102] demonstrated that elevated plasma levels of IL-6 and MMP-9 could accurately predict intra-amniotic infection even before PCR confirmation, increasing the positive predictive value to 96%. In a recent meta-analysis, Areia et al [63] reported that maternal procalcitonin exhibited an 82% sensitivity for detecting intra-amniotic infection, whereas PCR provided definitive molecular evidence of microbial etiology. Collectively, the combined application of PCR and inflammatory biomarkers establishes a more powerful predictive framework for identifying patients at risk of preterm birth and perinatal morbidity, thereby supporting earlier and more targeted clinical interventions.

F. Validity and Specificity in Normal Pregnancy

Liu et al [31] reported that amniotic fluid obtained from normal pregnancies is almost universally PCR-negative, suggesting that the physiologically healthy uterine environment is sterile. This observation underscores the high specificity of PCR (≥93%) and indicates a low probability of false-positive results when stringent quality control procedures are implemented [115], [116]. Similarly, the classic findings of Oh et al [105] revealed that approximately 24% of patients with a clinical diagnosis of chorioamnionitis showed no detectable microbial evidence, emphasizing the necessity of molecular confirmation prior to undertaking invasive therapeutic interventions.

G. Clinical Implications for High-Risk Pregnancy Management

The integration of PCR testing into risk-based antenatal screening programs represents a significant advancement in contemporary obstetric practice. Guo et al [106] demonstrated that PCR-based Non-Invasive Prenatal Testing (NIPT) is capable of detecting circulating microbial DNA in maternal blood, thereby introducing new opportunities for non-invasive prenatal screening. This combined molecular approach supports a paradigm shift from conventional, reactive diagnostics toward predictive and preventive obstetric care [107]. PCR is particularly crucial for diagnosing infections such as Cytomegalovirus (CMV) and Toxoplasma gondii, both of which are associated with severe congenital neurological abnormalities. Villar et al [24] and Sorrenti et al [55] confirmed that amniotic fluid PCR remains the gold standard for prenatal detection of CMV and toxoplasmosis, achieving sensitivities exceeding 90%. Moreover, the digitalization of diagnostic workflows has further accelerated clinical decision-making. With rapid turnaround times and minimal sample requirements, PCR-based testing now provides a practical and reliable point-of-care diagnostic tool for high-risk obstetric units [119], [120].

H. Limitations and Study Heterogeneity

Although this meta-analysis demonstrates the high diagnostic accuracy of PCR, moderate heterogeneity (I^2 = 46%) was observed across studies. This variability likely reflects differences in methodological design, specimen type (e.g., maternal blood versus amniotic fluid), and the specific PCR platforms utilized (conventional versus real-time). In several studies, incomplete quantitative data, such as true-positive, false-positive, false-negative, and true-negative values, may have limited the robustness of pooled statistical estimates. Additionally, the predominance of English-language publications from high-income settings introduces a potential source of publication bias, despite Egger's test indicating no significant effect ($p > 0.05$). To enhance external validity, future investigations should adopt multicenter cohort designs that directly compare multiple PCR modalities with other advanced molecular diagnostic tools, including next-generation sequencing

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(NGS). Incorporating machine learning algorithms into predictive modeling of obstetric complications could also enhance diagnostic precision and clinical applicability [110].

I. Final Synthesis

Overall, the present meta-analysis confirms that PCR remains the most sensitive and specific diagnostic modality for detecting intrauterine infections, outperforming both culture-based and serological methods [1], [27], [49]. Advances in next-generation PCR technologies including real-time, multiplex, nanopore, and digital PCR have significantly improved diagnostic speed, accuracy, and the capacity for polymicrobial detection [71]. Moreover, PCR positivity is strongly associated with major obstetric complications such as preterm labor, premature rupture of membranes (PROM), and low birth weight (LBW) [70], [79]. The integration of molecular detection with inflammatory biomarkers (e.g., IL-6, CRP, and procalcitonin) enhances predictive accuracy and provides a comprehensive clinical framework for early risk stratification [67], [74]. Collectively, these findings support the adoption of PCR-based diagnostics as a cornerstone of evidence-based maternal health care, reinforcing its role in predictive and preventive obstetric strategies to reduce perinatal morbidity and mortality.

V. CONCLUSION

PCR testing demonstrates excellent performance for the early detection of intrauterine infections in high-risk pregnancies, with pooled sensitivities and specificities of approximately 90% and 93%, respectively. Positive PCR results are significantly correlated with adverse pregnancy outcomes, particularly preterm birth and low birth weight. Emerging PCR technologies have reduced turnaround times and improved detection of polymicrobial infections, thereby strengthening their clinical utility in obstetric diagnostics. It is therefore recommended that PCR be implemented as an adjunct to risk-based antenatal screening programs, accompanied by rigorous laboratory validation to ensure diagnostic reliability. Future research should prioritize multicenter, prospective cohort studies that compare diverse molecular techniques, including next-generation sequencing and digital PCR, to refine diagnostic thresholds and improve predictive modeling. At the policy level, integrating PCR testing into national antenatal screening protocols represents a strategic step toward enhancing maternal-fetal outcomes through early detection and timely intervention.

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