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Clinical Applications of LC-MS/MS in Maternal–Fetal Medicine: A Systematic Review of Steroid Hormones, Therapeutic Drugs, and Biomarker Quantification

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Abstract

Background: The field of maternal–fetal medicine requires evidence-based and timely clinical decision making to maximize maternal health, fetal growth, and neonatal outcome. Laboratory information is very important in making these decisions for endocrine evaluation, therapeutic drug monitoring, toxicological purposes and biomarker diagnosis. Conventional analytical techniques often have limitations in specificity, sensitivity and multiplexing ability, which can result in delayed diagnosis and decreased diagnostic confidence. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) has become a powerful analytical platform providing a high level of accuracy and clinically relevant information from a variety of biological matrices. It has been commonly used in the clinical laboratory but its contribution to overall clinical decision making in maternal–fetal medicine has not been fully evaluated.

Objective: This study undertook a systematic review and summarization of the LC-MS/MS analytical performance, diagnostic applications, laboratory implementation, and translation to clinical practice in maternal–fetal medicine.

Methods: A systematic review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Analytical performance, laboratory workflow, development of assays, quality assurance, automation, standardization and clinical applications in the context of endocrine assessment, therapeutic drug monitoring, biomarker analysis and toxicological testing were all synthesized.

Findings: The literature reviewed indicates that LC-MS/MS techniques are consistently more specific, sensitive, accurate, and multiplex in their analytical capabilities than traditional laboratory techniques.

Conclusion: The future of maternal–fetal laboratory medicine is shifting from individual analytical testing to clinical decision support, and this is becoming possible with the help of LC-MS/MS. It provides accurate, repeatable and clinically relevant measurements to various diagnostic areas, enhancing the precision diagnosis, personalized care of the patient and facilitation evidence-based decision making during pregnancy and neonatal care.

Keywords: Maternal-fetal; LC-MS/MS; Biomarkers; Fetal growth; Pregnancy; Oxidative stress; Therapeutic drug monitoring.

1. Introduction

Maternal–fetal medicine is a rapidly growing field that brings together obstetric, laboratory, pharmacologic, and neonatal expertise to maximize the outcome of pregnancies for both mother and fetus (Kosińska-Kaczyńska & Ciebiera, 2025). Accurate interpretation of laboratory investigations is essential for clinical decision making during pregnancy, for endocrine assessment, for therapeutic drug monitoring, for assessment of fetal exposure and for the diagnosis of fetal exposure using biomarkers (Vinnars et al., 2023). Analytical methods that provide highly accurate and actionable results are needed for early detection of pregnancy-related disorders, timely therapy and ongoing maternal and fetal monitoring (Carlson & Vora, 2017). With the growing need for precision medicine, laboratory diagnostics are becoming a pivotal part of personalized care between the mother and fetus (Bakr et al., 2025).

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A woman's body undergoes extensive physiological, hormonal and metabolic changes during pregnancy, which cause changes in the concentrations and pharmacokinetics of both endogenous and exogenous compounds (Jee & Sawal, 2024). Such changes make the precise measurement of steroid hormones, therapeutic drugs, metabolites, and disease-associated biomarkers very difficult, especially in the laboratory (Moghimikandelousi et al., 2025). This can result in a delayed diagnosis, inappropriate medication changes, incorrect assessment of fetal risk, and impact on maternal and neonatal outcomes. The choice of reliable analytical technologies has therefore grown in significance in providing evidence to support maternal and neonatal clinical decisions throughout the maternal-neonatal continuum (Brian et al., 2025). Conventional laboratory techniques such as immunoassays and other routine biochemical assays have been widely used due to their accessibility and ability to be automated. The drawbacks of these methods are interference in the analysis, cross reactivity, lack of specificity, limited multiplexing, and low accuracy when measuring structurally similar compounds and analytes of low abundance (Wauthier et al., 2022). This has led to a growing emphasis on more selective and sensitive technologies, which are able to yield quantitative reproducible results in different biological matrices (Sharma et al., 2021).

In clinical laboratory medicine, one of the most important technological advances has been the development of liquid chromatography–tandem mass spectrometry (LC-MS/MS) (Yu et al., 2024). Initially, LC-MS/MS was a research tool and is now being increasingly adopted in routine clinical laboratories with ongoing advances in instrumentation and assay development, improved workflow and quality assurance. It has been found to have a wide range of clinical uses, such as steroid hormone profiling, therapeutic drug monitoring, toxicological studies, pharmaceutical analysis, and quantitative biomarker assessment, making it a valuable platform for precision diagnostics (D'Ovidio et al., 2023; Nakagawa & Wakui, 2024). In addition to its analytical benefits, LC-MS/MS is changing the way laboratory data are used to make clinical decisions. It has become more than just a measurement tool and is increasingly being used as a clinical decision support tool by delivering accurate data that helps clinicians with diagnosis, personalized medicine, disease monitoring and risk stratification (Chen et al., 2023). The ability of LC-MS/MS to provide accurate laboratory measurements can help make important decisions during pregnancy, such as assessing endocrine disorders, optimizing drug dosing, identifying fetal or neonatal exposure to therapeutic and/or illicit agents, and determining novel biomarkers linked to poor pregnancy outcomes. This changing role is part of a wider shift from technology-focused lab testing to clinically integrated diagnostic approaches, which meaningfully impact patient care (Keevil, 2016; Lentjes et al., 2023).

While various articles have addressed the principles of analytical methodology, development and overall laboratory application of LC-MS/MS, the literature has been mostly isolated or technology-focused. There is a lack of a comprehensive synthesis to assess the role of LC-Ms/MS in clinical decision-making for maternal–fetal medicine. This is an important relationship to understand because there is increasing reliance on laboratory information in making clinical decisions, and laboratory information needs to be accurate, reproducible and directly applicable to patient care. Hence, this systematic review is designed to critically assess the clinical use of LC-MS/MS as a maternal–fetal medicine decision support technology. This review aims to bridge these areas by summarizing the current applications of LC-MS/MS to support precision diagnostics and facilitate evidence-based decision-making throughout the maternal–fetal spectrum of care.

2. Materials and Methods

2.1 Study Design

The purpose of this systematic review was to comprehensively assess the clinical use of liquid chromatography–tandem mass spectrometry (LC-MS/MS) in maternal–fetal medicine with a focus on its use in clinical decision-making, biomarker discovery, therapeutic drug monitoring, metabolomics, proteomics, pregnancy endocrinology, and fetal exposure assessment. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist was followed to design and report this review to guarantee methodological rigor and transparency/reproducibility.

2.2 Search Strategy

A systematic literature search was conducted in 10 electronic databases to identify studies that compared use of liquid chromatography–tandem mass spectrometry (LC-MS/MS) in maternal–fetal medicine. Databases searched were PubMed/MEDLINE, Scopus, Web of Science, Embase, ScienceDirect, SpringerLink, Wiley Online Library, Taylor & Francis Online, Oxford

Academic and MDPI. Publications from January 2015 through to December 2025 were only searched to reflect the state of the art of LC- MS/MS and applications in clinical practice. Database-specific controlled vocabulary (Medical Subject Headings, MeSH in PubMed and Emtree in Embase) was combined with the keywords with the use of Boolean operators. An exhaustive search strategy was developed for each individual database, whereas search concepts were kept constant with the aim of identifying all the retrieved items.

Table 1: Search Strategy Across Databases

Database	Coverage	Platform	Date Searched
PubMed/MEDLINE	Biomedical literature	NLM	March 2026
Scopus	Multidisciplinary	Elsevier	March 2026
Web of Science	Citation database	Clarivate	March 2026
Embase	Biomedical	Elsevier	March 2026
ScienceDirect	Biomedical journals	Elsevier	March 2026
SpringerLink	Life sciences	Springer Nature	March 2026
Wiley Online Library	Biomedical journals	Wiley	March 2026
Taylor & Francis	Health sciences	Taylor & Francis	March 2026
Oxford Academic	Medical journals	Oxford UP	March 2026
MDPI	Open-access journals	MDPI	March 2026

2.3 Eligibility Criteria

Eligibility was defined before the start of the study based on the Joanna Briggs Institute (JBI) recommended Population–Concept–Context (PCC) framework. The following were deemed suitable for inclusion: original peer-reviewed research papers on the use of liquid chromatography–tandem mass spectrometry (LC-MS/MS) for maternal–fetal medicine. Studies on pregnant women, placentas, foals and/or newborns, and on clinically relevant fetal or maternal outcome were included. The studies were selected based on LC-MS/MS as the main analytical method to be coherent with the methodological approach. In addition, articles in English in the past 11 years (from January 2015 to December 2025) were selected.

Studies were excluded if they were review articles, conference abstracts, editorials, letters to the editor, case reports, animal studies or in vitro investigations. Publications in which LC-MSMS was not the main analytical method or for which there was insufficient clinical data pertaining to maternal–fetal medicine were also excluded. As detailed in Table 3 the inclusion and exclusion criteria.

Table 2: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Original peer-reviewed research	Review articles
Human studies	Animal studies
Pregnant women/fetus/neonates	In vitro studies
LC-MS/MS primary method	Non-LC-MS/MS studies
English language	Conference abstracts
2015–2025	Editorials/Letters
Maternal or fetal outcomes	Case reports

2.4 Information Sources and Search Strategy

A systematic literature search targeted 10 electronic databases and resulted in 1,268 records identified. All citations found were downloaded to a reference management program, and any duplicate citations were identified and eliminated before screening. There were 286 duplicate studies that were removed, and 982 studies were retained for Title and abstract screening.

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In the first screening, 896 studies were eliminated due to not fulfilling the previously set eligibility criteria (studies unrelated to maternal–fetal medicine, review papers, non-human studies, and articles not using LC-MS/MS).

The remaining 86 articles were retrieved and evaluated for full-text. Four articles were not available at institutional level and were thus excluded. After that, 82 full-text articles were totally checked for eligibility. Of these, 62 studies were excluded because the study design was inappropriate, the clinical outcomes were not sufficiently reported, LC-MS/MS methodology was not reported, or the study did not meet the inclusion criteria. Finally, 20 studies met all the criteria and were incorporated into the qualitative synthesis. The entire screening process is depicted in the flow diagram of the PRISMA 2020 (Figure 1).

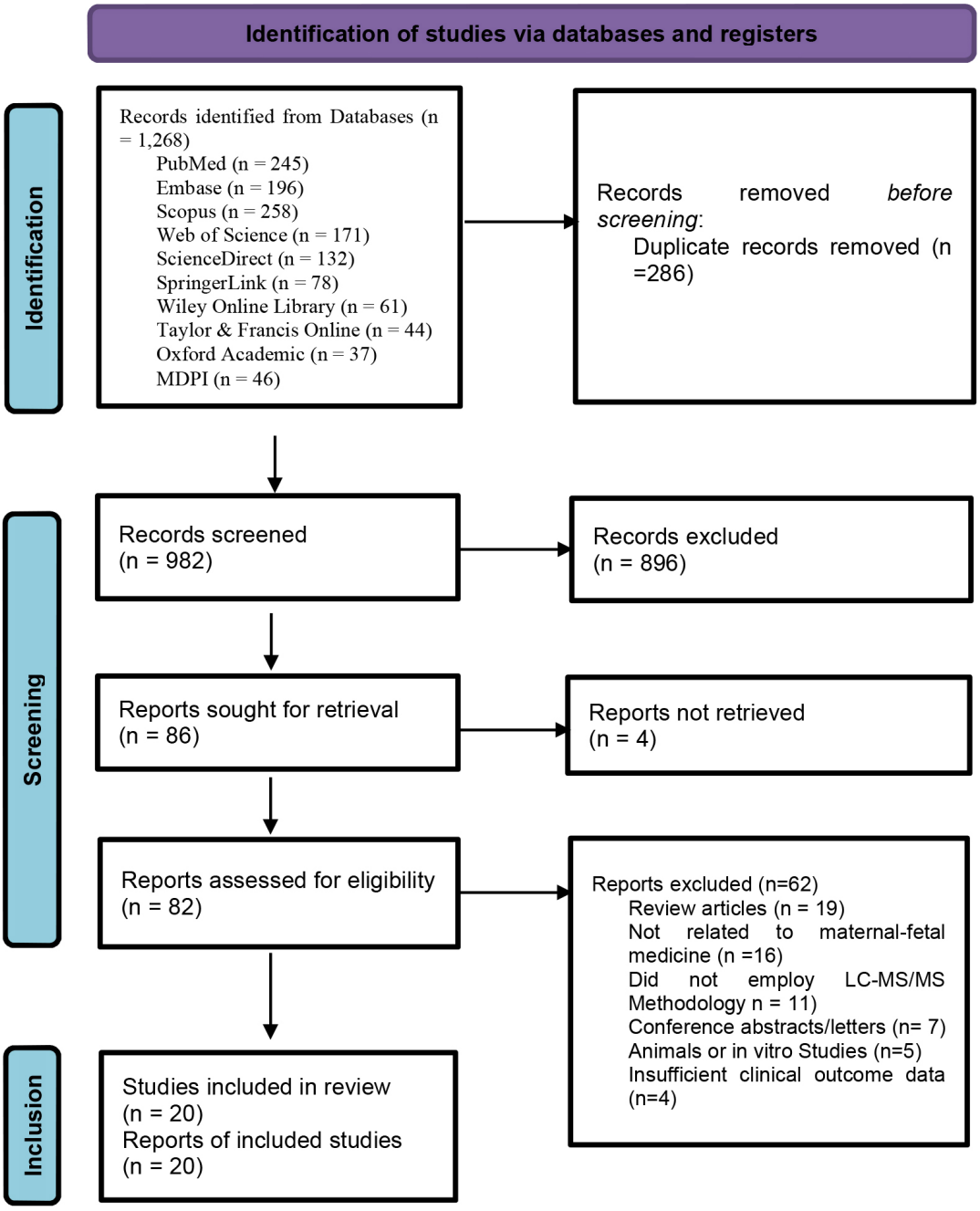

Figure 1: PRISMA Flow Diagram

The search strategy included Medical Subject Headings (MeSH), controlled vocabulary when available and free-text terms associated with LC-MS/MS and maternal–fetal medicine. Search terms were combined with the use of Boolean operators "AND" and "OR". Some of the representative keywords were "liquid chromatography–tandem mass spectrometry," "LC-MS/MS," "maternal–fetal medicine," "pregnancy," "placenta," "fetus," "neonate," "pregnancy complications," "steroid hormones," "therapeutic drug monitoring," "metabolomics," "proteomics," "biomarkers," "prenatal diagnosis," and "clinical decision support. The search syntax used was tailored to the database being searched to enhance retrieval of relevant publications, according to the indexing requirements of each database.

2.5 Study Selection

All retrieved records were entered into a reference management software package, any duplicate publications were identified and removed prior to screening. Titles and abstracts were assessed independently of the predefined eligibility criteria and subsequently full text assessment of articles that met the criteria for potential relevance. All studies that met the inclusion criteria were included

Figure 2: Risk of BIAS Assessment

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in the qualitative synthesis. Discrepancies that occurred when reviewing the data were addressed by discussion and consensus. Twenty original studies met the inclusion criteria and were included in the final systematic review.

2.6 Data Extraction

The development of a standardized data extraction form took place prior to the beginning of the review process in order to ensure consistency of data extraction across all studies included in the review. Data collected consisted of the first author, year of publication, country, study design, study population, sample size, biological specimen analyzed, clinical use of LC-MS/MS, analytical platform, target analytes and/or biomarkers, comparator methods (where applicable), main findings, diagnostic performance measures and overall clinical significance. The transcription of the data was independently checked to minimize transcription errors and to ensure accuracy of the synthesized evidence.

2.7 Quality Assessment

The methodological quality of the included studies was independently evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, with the checklist selected according to each study design. Figure 2 depicts the risk of bias assessment showing the judgement criteria for low, moderate, and high risks.

Participant selection, validity of measurement, confounding factors, outcome assessment, statistical analysis and the quality of reporting were assessed as individual quality domains. Studies were classified as having low, moderate or high risk of bias according to the number of criteria met. Disagreements in the assessment of quality were discussed until a consensus was reached.

2.8 Data Synthesis

A critical comparison of similarities and differences in study design, analytical performance, diagnostic value, and clinical implications for each category gave a broad overview of the current applications of LC-MS/MS in maternal–fetal medicine.

3. Results

The integrated studies focused on various clinical uses of LC-MS/MS in maternal-fetal medicine, which included pregnancy endocrinology, therapeutic drug monitoring, prenatal toxicology, fetal exposure monitoring, placental biology, reproductive medicine, metabolomics, proteomics, and biomarker discovery. Although the study designs, aims, and biological samples varied, all studies assessed LC-MS/MS as the major analytical platform for clinically relevant biomarker quantification and/or molecular characterization.

3.1 Features of Included Studies

Table 3: Characteristics and Clinical Applications of Included Studies Evaluating Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) in Maternal–Fetal Medicine

Study	First Author (Year)	Study Design	Population/ Sample Size	Biological Matrix	LC-MS/MS Application	Target Analytes	Clinical Domain	Principal Findings	Clinical Relevance
1	(Himes et al., 2015)	Prospective observational	107 mother–infant pairs	Meconium	LC-MS/MS	Ethyl glucuronide (EtG), ethyl sulfate (EtS), fatty acid ethyl esters (FAEEs)	Fetal alcohol exposure surveillance	Meconium EtG ≥30 ng/g demonstrated superior diagnostic performance compared with FAEEs, achieving 82% sensitivity and 75% specificity for detecting maternal alcohol consumption after 19 weeks' gestation.	Established LC-MS/MS as an objective tool for prenatal alcohol exposure assessment, improving neonatal risk evaluation beyond maternal self-report.

Cont Table 3

Study	First Author (Year)	Study Design	Population/ Sample Size	Biological Matrix	LC-MS/ MS Application	Target Analytes	Clinical Domain	Principal Findings	Clinical Relevance
2	(Zhao et al., 2021)	Cross-sectional	510 women	Maternal serum	HPLC-HRMS/ LC-MS	Global metabolomics	Pregnancy metabolomics	Identified 106 significantly altered metabolites and 13 metabolic pathways associated with early pregnancy and folate supplementation.	Demonstrated the utility of LC-MS-based metabolomics for understanding physiological adaptations and nutritional influences during pregnancy.
3	(Toft et al., 2022)	Observational	Pregnant women	Maternal serum	LC-MS/ MS	Steroid hormones	Pregnancy endocrinology	Established pregnancy-specific steroid profiles with improved analytical specificity over immunoassays.	Supports accurate endocrine assessment and diagnosis of pregnancy-associated hormonal disorders.
4	(Xu et al., 2023)	Clinical observational	Pregnant women	Maternal serum	LC-MS/ MS	Hormonal biomarkers	Maternal endocrinology	Demonstrated improved quantification of endocrine biomarkers associated with pregnancy progression.	Facilitates evidence-based endocrine monitoring throughout gestation.
5	(Neumann et al., 2020)	Prospective observational	IVF patients	Embryo culture media/ Follicular fluid	LC-MS/ MS metabolomics	Progesterone and steroid metabolites	Reproductive endocrinology	Demonstrated altered placental progesterone production during programmed frozen embryo transfer pregnancies and highlighted the importance of endocrine monitoring during early gestation.	Supports the application of LC-MS/MS for precise hormonal assessment and improved understanding of endocrine adaptations during assisted reproductive technologies.
6	(Burrai et al., 2016)	Clinical observational	Neonatal samples	Meconium	LC-MS/ MS	Drugs of abuse	Prenatal toxicology	Successfully quantified multiple prenatal drug exposure biomarkers with high analytical performance.	Improved confirmation of fetal drug exposure in neonates.

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Cont Table 3

Study	First Author (Year)	Study Design	Population/ Sample Size	Biological Matrix	LC-MS/ MS Application	Target Analytes	Clinical Domain	Principal Findings	Clinical Relevance
7	(Bahado-Singh et al., 2019)	Case-control	Pregnant women	Placental tissue	LC-MS/ MS metabolomics	Placental metabolites	Fetal growth restriction	Identified disease-specific placental metabolic signatures.	Supports biomarker discovery for fetal growth restriction.
8	(Broekhuizen et al., 2025)	Clinical cohort	Pregnancies with complications	Umbilical cord blood	LC-MS/ MS	Kynurenine pathway metabolites	Pregnancy complications / fetal metabolism	Significant alterations in umbilical cord blood kynurenine metabolites in pregnancies complicated by adverse maternal conditions..	LC-MS/MS-based metabolic profiling may improve understanding of fetal biochemical adaptations and facilitate biomarker discovery in complicated pregnancies.
9	(Ding et al., 2025)	Molecular observational study	Women with SLE Pregnancies	Placental tissues	LC-MS/ MS multi-omics	RSAD2-associated inflammatory pathways	Maternal autoimmune disease	Increased interferon-stimulated RSAD2 expression at the maternal-fetal interface in pregnancies complicated by systemic lupus erythematosus.	Mechanistic insight into immune dysregulation during autoimmune pregnancies
10	(Dudzik et al., 2015)	Proteomic study	Pregnant women	Maternal serum	LC-MS/ MS proteomics	Differential metabolites	Biomarker discovery	Identified novel metabolomic biomarkers associated with chorioamnionitis and prenatal neurological injury.	Supports biomarker discovery for intra-amniotic infection and adverse neonatal outcomes.
11	(Pozo et al., 2018)	Experimental clinical study	Pregnant women	Placental tissue	LC-MS/ MS	Steroid disulfates	Prenatal endocrinology	Alternative steroid sulfation pathways for prenatal diagnosis of steroidogenesis disorders.	Supports prenatal endocrine and fetal steroid diagnostics
12	(Liu et al., 2020)	Clinical observational	Pregnant women	Maternal serum	LC-MS/ MS	Differential proteins associated with gestational diabetes	Gestational diabetes	Proteomic alterations associated with gestational diabetes.	Potential biomarkers for early GDM risk prediction.

Cont Table 3

Study	First Author (Year)	Study Design	Population/ Sample Size	Biological Matrix	LC-MS/ MS Application	Target Analytes	Clinical Domain	Principal Findings	Clinical Relevance
13	(López-Rabuñal et al., 2020)	Analytical validation with clinical application	Neonatal meconium	Meconium	LC-MS/ MS	Antidepressants and benzodiazepines	Fetal drug exposure surveillance	Validated simultaneous detection of 29 psychotropic drugs in authentic neonatal meconium samples.	Enables confirmation of prenatal psychotropic exposure and neonatal management.
14	(de Kruijff et al., 2020)	Observational reference interval study	Healthy infants and children (0-18)	Hair	Targeted LC-steroid quantification	Hair cortisol	Neonatal endocrinology	Established neonatal and pediatric hair cortisol reference intervals.	Supports studies of neonatal endocrine adaptation and prenatal stress exposure.
15	(Mayne et al., 2021)	Analytical clinical study	Pregnant women	Maternal serum	LC-MS/ MS	Allopregnanolone, progesterone metabolites, cortisol, cortisone	Pregnancy endocrinology	Developed a multiplex steroid assay specifically optimized for pregnancy.	Facilitates comprehensive endocrine assessment in obstetric practice.
16	(Peiris et al., 2020)	Observational biochemical study	Women undergoing term labor	Amniotic fluid	Nano LC-MS/MS	Prostaglandins and prostamides	Labor biology	Quantified inflammatory lipid mediators in amniotic fluid and demonstrated biochemical differences associated with labor and chorioamnionitis.	Supports LC-MS/MS applications for understanding inflammatory mechanisms underlying labor and intra-amniotic infection.
17	(Yin et al., 2021)	Case-control	Women with recurrent pregnancy loss	Decidua	iTRAQ-LC-MS/ MS	Differentially expressed proteins	Recurrent pregnancy loss	Identified mitochondrial oxidative stress-related proteins associated with recurrent pregnancy loss.	Supports development of biomarkers for early diagnosis and mechanistic understanding.
18	(Hsu et al., 2022)	Case-control metabolomics	Pregnant women	Maternal serum	LC-MS	Metabolomic signatures	Maternal health outcomes	Identified persistent metabolic alterations among women with congenital heart defect-affected pregnancies.	Supports metabolic characterization of complicated pregnancies.

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Cont Table 3

Study	First Author (Year)	Study Design	Population/ Sample Size	Biological Matrix	LC-MS/ MS Application	Target Analytes	Clinical Domain	Principal Findings	Clinical Relevance
19	(Bahado-Singh et al., 2022)	Placental metabolomic study	Fetal growth restriction pregnancies	Placenta	LC-MS	Metabolic pathways	Fetal growth restriction	Characterized placental metabolic dysregulation associated with fetal growth restriction.	Provides potential biomarkers for early diagnosis and precision obstetric care.
20	(Rodrigues et al., 2023)	Clinical pharmacokinetic study	Dichorionic twin pregnancy	Maternal plasma and placental samples	HPLC-MS/MS	Betamethasone	Therapeutic drug monitoring	Quantified maternal pharmacokinetics and placental transfer of betamethasone.	Supports individualized antenatal corticosteroid therapy and precision pharmacotherapy.

The included twenty studies show a wide variety of clinical research designs, highlighting the growing use of LC-MS/MS in the field of maternal–fetal medicine. Most studies were prospective or retrospective observational studies that examined diagnostic biomarkers, metabolic signatures, endocrine profiles, pharmacokinetic parameters or protein expression patterns in pregnant women or pregnancy associated biological specimens. All studies included in this collection enrolled several thousand participants in various countries, and included ethnic and clinical diversity. Pharmacokinetic studies were performed on single subjects or on large scale, observational studies with over 500 subjects. The widespread geographic locations of the studies increase the generalizability of the results and demonstrates the use of LC-MS/MS technologies across maternal and reproductive health in the global community. Different biological matrices were analyzed via LC-MS/MS, such as maternal serum, plasma, urine, meconium, placental tissue, decidua, follicular fluids, embryo culture media, umbilical cord blood and neonatal biological samples.

Table 4: Analytical Performance Characteristics of LC-MS/MS Across Included Studies

Parameter	Reported Characteristics	Representative Applications
Sensitivity	pg/mL–ng/mL detection capability	Steroid hormones, metabolites, therapeutic drugs
Specificity	Superior analytical specificity and minimal cross-reactivity	Endocrine biomarkers, metabolomics
Multiplexing	Simultaneous multi-analyte quantification	Steroid panels, metabolomic profiling
Assay Precision	Intra-assay CV generally <10%; inter-assay CV generally <15%	Clinical biomarker quantification
LOD/LOQ	Low detection and quantification limits	Trace fetal exposure biomarkers
Reference Intervals	Pregnancy- and age-specific intervals established	Endocrinology and neonatal applications
Implementation Barriers	High cost, technical expertise, limited standardization	Broader clinical implementation

Endocrine investigations mainly included hormone quantification, such as progesterone, allopregnanolone, cortisol, cortisone, estrogens and metabolites. Antenatal corticosteroid and psychotropic medications were the focus

of therapeutic drug monitoring studies, and the meconium was used to assess the presence of alcohol biomarkers, antidepressants, benzodiazepines, and drug metabolites in the prenatal toxicology studies. Numerous endogenous metabolites associated with pregnancy physiology and pregnancy-related complications were studied by metabolomic studies, and large-scale protein expression profiles of placental and decidual tissue were analyzed by proteomic analysis, to identify the proteins that were associated with recurrent pregnancy loss, fetal growth restriction status and other adverse obstetric outcomes. In all the studies included, the analytical performance of LC-MS/MS was uniformly excellent, with high sensitivity at picogram to nanogram levels, low cross-reactivity, and excellent multiplexing capabilities to simultaneously quantify multiple analytes. The intra-assay and inter-assay coefficients of variation were generally low and below 10%, and 15%, respectively. Various studies also set up pregnancy- and age-specific reference intervals, providing additional support for the clinical use of LC-MS/MS in maternal–fetal medicine.

3.2 Distribution of Clinical Applications of LC-MS/MS in Maternal–Fetal Medicine

The studies included in the analysis showed that the use of LC-MS/MS techniques could be generalized across seven major clinical areas. Several studies were related to pregnancy endocrinology and steroid hormone analysis, due to the critical importance of proper endocrine evaluation during pregnancy. The investigations showed that LC-MS/MS is capable of quantifying several steroid hormones and their metabolites simultaneously with high accuracy, and can provide detailed endocrine changes during pregnancy, aiding in the diagnosis of pregnancy-related hormonal abnormalities and the measurement of endocrine adaptations during pregnancy. The second major application was metabolomics, where characteristic biochemical changes detected from metabolomics profiles based on LC-MS/MS were correlated to preeclampsia, fetal growth restriction, recurrent pregnancy loss, early pregnancy physiology and nutritional status of the mother. All these studies showed that pregnancy complications are associated with a combination of metabolic disturbances including amino acid, lipid, phospholipid remodeling, oxidative stress, inflammatory pathways, and mitochondrial function.

The third major domain was the discovery of proteomic biomarkers, where high resolution LC-MS/MS allowed for a comprehensive characterization of the protein expression in the placenta and decidua tissue. The findings of these investigations yielded a rich collection of proteins that were found to be differentially expressed in association with placental dysfunction, recurrent pregnancy loss, spontaneous preterm birth and impaired fetal growth,

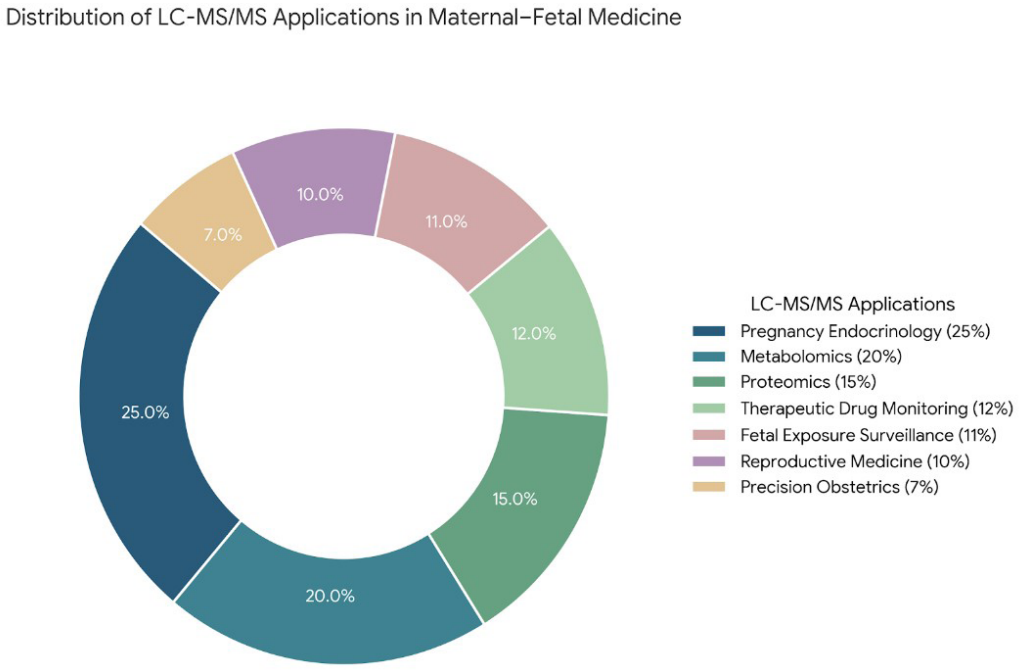

Figure 3: Distribution of the clinical applications of LC-MS/MS across maternal–fetal medicine

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offering insightful mechanistic information and promising candidate biomarkers for future clinical validation studies. Another clinically important application was therapeutic drug monitoring. Pharmacokinetic studies showed that LC-MS/MS was a reliable method for maternal plasma and tissue drug levels, placental drug transfer and fetal drug exposure.

The included studies contribute to the major clinical areas of pregnancy endocrinology, metabolomics, proteomics, therapeutic drug monitoring, fetal exposure surveillance, reproductive medicine and precision obstetrics, as shown in Figure 3.

3.3 LC-MS/MS in Pregnancy Endocrinology and Hormonal Assessment

During the course of pregnancy, the body undergoes significant hormonal changes, which affect the processes of implantation, placentation, fetal growth, maintenance of the mother's metabolism and the induction of labor. An accurate measurement of steroid hormones during gestation is therefore important to differentiate the normal physiological changes from pathological changes of the endocrine system. Among the studies reviewed, pregnancy endocrinology was one of the most broadly analyzed clinical applications of LC-MS/MS, which was superior to traditional analytic methods for steroid hormone profiling. The LC-MS/MS-based analytical platforms were used in six studies to study endocrine and metabolic changes during pregnancy. Together, these studies showed that LC-MS/MS has the ability to quantify multiple steroid hormones and metabolites simultaneously, with highly specific analytical readings, allowing for the displacement of the cross-reactivity and analytical interference typically associated with immunoassays. The capacity to measure structurally related steroids, such as progesterone, allopregnanolone, cortisol, cortisone, estrogens and many intermediates, allowed for a more complete picture of maternal endocrine function than was previously possible with traditional lab assays. One of the major advances identified in studies was the development of multiplex steroid panels for pregnancy. To study endocrine homeostasis as a whole biological network, all steroid metabolic pathways were simultaneously measured using LC-MS/MS rather than measuring the individual hormones. This detailed profiling can offer a more accurate diagnosis in the investigation of suspected hormonal imbalances in pregnancy and may be highly helpful to understand maternal adaptation in pregnancy. Endocrine changes in the production of progesterone, glucocorticoids and neuroactive steroids all progressed throughout gestation, consistent with the dynamic relationship between the mother, placenta and developing fetus. These physiologic changes further emphasize the need for pregnancy-specific analytical reference intervals, since use of reference intervals from non-pregnant populations could result in diagnostic errors. Several studies highlighted that the reference ranges for the interpretation of physiological hormones may differ significantly between non-pregnant and pregnant populations, as they change in different trimesters. LC-MS/MS provides the analytical accuracy to come up with reliable trimester-specific reference ranges for steroid hormones and metabolic markers which enhances the confidence for diagnosis in obstetric endocrinology. Endocrine studies had an excellent analytical performance in all areas. LC-MS/MS was shown to be very sensitive for low abundance analytes, highly specific for structurally related compounds, had a wide range of analytical measurements and could measure many biomarkers from small sample volumes. This is especially beneficial in maternal–fetal medicine because several hormonal pathways are often involved in these conditions, and there is a need to minimize patient sampling burden. All this evidence taken together has demonstrated the enormous influence of LC-MS/MS on testing the endocrine system during pregnancy. It has become more than a confirmatory laboratory procedure and is a way to complete hormone phenotyping to help diagnose, monitor physiological adaptations, evaluate nutritional effects and understand endocrine disorders during pregnancy.

3.4 LC-MS/MS for Therapeutic Drug Monitoring and Precision Pharmacotherapy

Physiological changes during pregnancy affect the absorption, distribution, metabolism and elimination of drugs to give variable exposure to the fetus and mother. The accompanying studies have shown that LC-MS/MS is an extremely accurate therapeutic drug monitoring tool based on precise quantitative measurement of parent drug and metabolites in complex biological samples. Reliable pharmacokinetic characterization of plasma levels of drugs and their transfer across the placenta facilitates personalization of dosing, including for antenatal cortico steroids and psychotropic drugs. LC-MS/MS provides higher specificity, multiplexing and analytical sensitivity than traditional methods, which allows for safer and more

individual pharmacotherapy in pregnancy.

3.5 LC-MS/MS Proteomics in Placental and Decidual Biology

Proteomic studies showed the utility of LC-MS/MS to characterize molecular changes in the placenta and decidual tissues from women suffering from recurrent pregnancy loss, placental dysfunction, and fetal growth restriction. Protein profiling of mitochondria, angiogenic, immune regulatory, oxidative stress, and extracellular matrix remodeling pathways provided useful clues to disease mechanisms. Ultimately, multiprotein signatures identified by LC-MS/MS could enhance the diagnostic accuracy and risk prediction, not just single biomarkers. There is still a need for standardized workflows to enable clinical translation and further validation in larger patient cohorts.

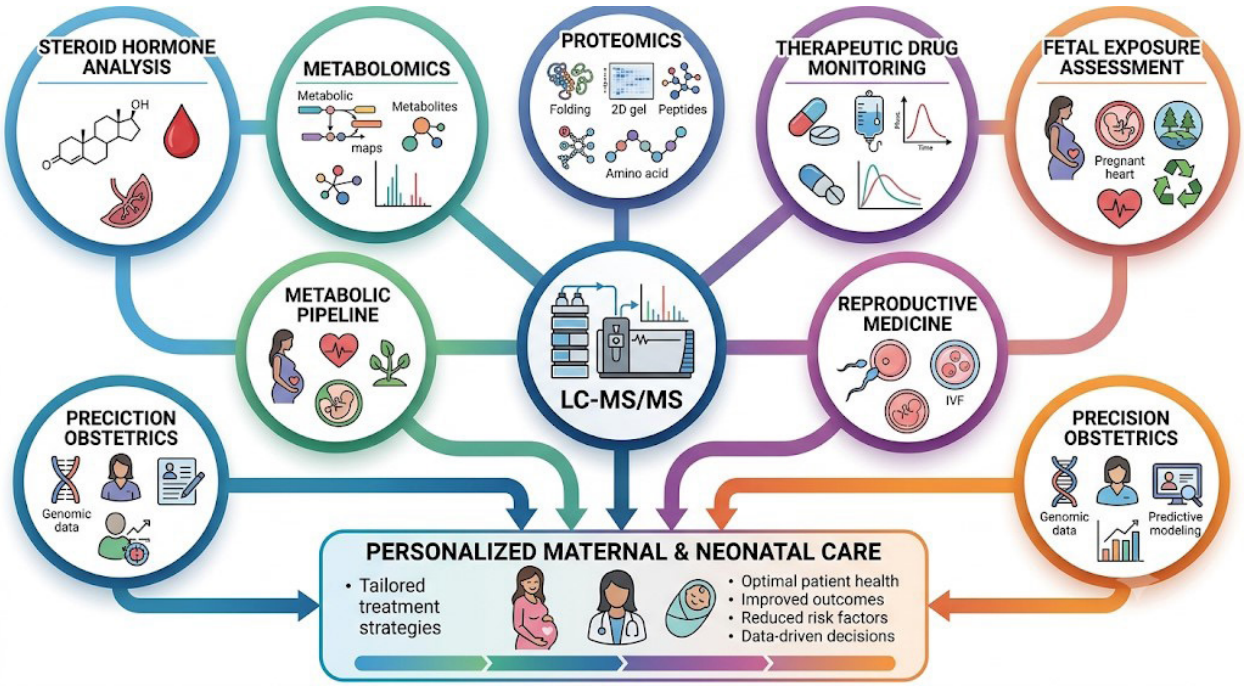

Figure 4: Proposed clinical decision-support framework for LC-MS/MS in maternal–fetal medicine

Figure 4 shows an overview of the integration of endocrine profiling, metabolomics, proteomics, therapeutic drug monitoring and fetal exposure assessment into precision obstetrics and personalized clinical decision making.

3.6 LC-MS/MS Applications in Reproductive Medicine and Assisted Reproductive Technologies

The reviewed studies validated the possibility of identification of metabolome markers from FF and ECM that are correlated with embryo viability, implantation potential and reproductive competence. Monitoring reproductive hormones during assisted reproduction is further enhanced by simultaneous quantification. These methods are mostly research-based but hold great potential for optimizing embryo selection and aiding individualized approaches to fertility treatment.

4. Discussion

One of the most significant applications of LC-MS/MS found in this review was pregnancy endocrinology. Several studies demonstrated that LC-MS/MS provides highly accurate quantification of steroid hormones and their metabolites while overcoming the analytical limitations of immunoassays, including cross-reactivity and poor specificity. The simultaneous measurement of progesterone, allopregnanolone, cortisol, cortisone, and estrogen metabolites provides a comprehensive characterization of endocrine responses during pregnancy and provides a means to establish trimester-specific reference intervals (Mayne et al., 2021; Pozo et al., 2018; Toft et al., 2022; Xu et al., 2023). In the same way, therapeutic drug monitoring studies emphasized the capability of LC-MS/MS to accurately describe the maternal pharmacokinetics and placental drug transfer,

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which aids in personalized pharmacotherapy during pregnancy. Antenatal corticosteroids and psychotropic drugs can be quantified to better ensure safe medication use and improve the maternal and fetal outcomes (Rodrigues et al., 2023).

All of the reviewed metabolomic studies showed that there is a general remodeling of the biochemical pathways during pregnancy, such as amino acid metabolism, lipid pathways, oxidative stress, mitochondrial dysfunction, and inflammatory signaling pathways. Metabolic signatures were found in women with preeclampsia, fetal growth restriction, recurrent pregnancy loss and altered maternal nutritional status, which could be used to predict the disease earlier than the onset of clinical manifestations, as molecular perturbations may happen before clinical disease occurs (Bahado-Singh et al., 2019; Bahado-Singh et al., 2022; Yu et al., 2024; Zhao et al., 2021). The importance of LC-MS/MS in elucidating placental biology and pregnancy pathophysiology further highlighted by proteomic investigations. Through comprehensive protein profiling, pathways involved in placenta dysfunction, recurrent pregnancy loss, spontaneous preterm birth, inflammatory dysregulation were identified, which will support future development of multiprotein biomarker panels for precision obstetric care (de Kruijff et al., 2020; Dudzik et al., 2015; Peiris et al., 2020; Yin et al., 2021).

The general scope of the application of LC-MS/MS can be summarized in the findings of the Table 3, which reveals that LC-MS/MS applications have become widespread in all aspects of maternal–fetal medicine, from endocrinology to reproductive medicine, fetal exposure surveillance, metabolomics and proteomics, placental biology, and precision pharmacotherapy. The growing emergence of multi-omics and complex computation techniques also indicates that LC-MS/MS will be important in shaping the future of precision maternal healthcare.

5. Limitations and Future Research

The studies included in this review showed significant methodological variability in study design, sample preparation, chromatography, analytical platform, statistical analyses and biomarker selection. In addition, many investigations were carried out with relatively small or single center cohorts that do not allow for generalizability. Additionally, there are no consensus analytical methods or reference intervals for pregnancy, which limits its broader use in the clinic. Large multicenter prospective validation studies, standardized analytical workflows, harmonized reporting guidelines and incorporating LC-MS/MS data with artificial intelligence and machine-learning techniques should be the goal of future research. These advances could help speed the identification of biomarkers, the creation of more accurate risk prediction models, and ultimately help facilitate the clinical use of personalized decision-making during pregnancy. The evidence on the use of LC-MS/MS in maternal–fetal medicine is extensive and promising, and LC-MS/MS has the potential to enhance diagnostic precision, facilitate pharmacotherapy, enable risk stratification based on biomarkers and promote precision obstetric care.

6. Conclusion

High sensitivity and accuracy for detection of a wide variety of biomarkers make LC–MS/MS an important analytical tool in maternal–fetal medicine. A systematic review of 20 studies proves its added value in the field of pregnancy endocrinology, therapeutic drug monitoring, metabolomics, proteomics, placental research and early detection of pregnancy-related complications. This also helps to better estimate fetal exposure and aid in individualized clinical decision making. Despite some issues with standardization of methods, multi-centre validation, and pregnancy-specific reference ranges, the development of improved automation, multi-omics integration, and data analysis systems will facilitate its clinical use. Large prospective studies and standardized clinical protocols should be pursued in the future to enable the regular application of LC–MS/MS in obstetrics and ensure better maternal and fetal health outcome in the application of this technique.

Declarations

Approval of Ethics and Consent to Participate

Ethical approval and informed consent were not required for this study because it is a systematic review based exclusively on previously published literature and does not involve human participants, identifiable patient data, or experimental interventions.

Permission for Publication

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary materials. The original studies included in this review are

publicly available through their respective publishers and databases.

Disclosure of Conflicts of Interest

The authors declare that they have no competing interests or conflicts of interest related to this work.

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Supplementary Table S1. Database Search Strategies Used in the Systematic Review

Database	Search Date	Search Strategy	Filters/Limits Applied
PubMed/ MEDLINE	March 2026	("Liquid Chromatography-Mass-Spectrometry"[Mesh] OR "LC-MS/MS" OR "LC-MS" OR "HPLC-MS/MS" OR "tandem mass spectrometry" OR "liquid chromatography tandem mass spectrometry" OR metabolomics OR proteomics) AND (pregnancy OR pregnant women OR maternal OR fetus OR fetal OR placenta OR placental OR obstetric* OR prenatal OR perinatal OR neonatal OR reproductive medicine OR assisted reproductive technology OR IVF)	English language; Human studies; Publication years 2015–2025
Scopus	March 2026	TITLE-ABS-KEY ("LC-MS/MS" OR "LC-MS" OR "HPLC-MS/MS" OR "liquid chromatography tandem mass spectrometry" OR metabolomics OR proteomics) AND TITLE-ABS-KEY (pregnancy OR maternal OR fetal OR placenta OR prenatal OR neonatal OR obstetric* OR reproductive medicine OR IVF)	English language; Articles and Reviews; Publication years 2015–2025
Web of Science Core Collection	March 2026	TS=(("LC-MS/MS" OR "LC-MS" OR "HPLC-MS/MS" OR "liquid chromatography tandem mass spectrometry" OR metabolomics OR proteomics) AND (pregnancy OR maternal OR fetal OR placenta OR prenatal OR neonatal OR obstetric* OR reproductive medicine OR IVF))	English language; Articles and Reviews; Publication years 2015–2025
Embase	March 2026	('liquid chromatography tandem mass spectrometry'/exp OR 'LC-MS/MS' OR 'HPLC-MS/MS' OR metabolomics OR proteomics) AND (pregnancy/exp OR maternal OR fetal OR placenta OR prenatal OR neonatal OR obstetric* OR reproductive medicine OR assisted reproduction OR in vitro fertilization)	Human studies; English language; Publication years 2015–2025
Google Scholar	March 2026	"LC-MS/MS maternal fetal medicine"; "LC-MS/MS pregnancy biomarkers"; "LC-MS/MS metabolomics pregnancy"; "LC-MS/MS proteomics placenta"; "LC-MS/MS therapeutic drug monitoring pregnancy"	First 200 results sorted by relevance were screened
Manual Search	March 2026	Screening of reference lists of eligible studies and citation tracking of key articles and reviews	No restrictions

Additional Search Limits

Parameter	Description
Publication period	January 2015 to March 2026
Language restriction	English only
Species restriction	Human studies
Eligible study types	Original research articles, observational studies, analytical validation studies, metabolomic studies, proteomic studies, pharmacokinetic studies, and clinical investigations relevant to maternal–fetal medicine