Saroha et al. Scr Med. 2026 Jan-Feb;57(1):103-20. DOI:10.5937/scriptamed57-58977

REVIEW ARTICLE

Pharmacotherapeutic Strategies in High-Risk Pregnancy: Balancing Maternal and Foetal Safety

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Abstract

Pharmacotherapy in high-risk pregnancies necessitates customised, evidence-based strategies to provide optimal results for women and their infants. A keen awareness that physiological changes during pregnancy can affect medication pharmacokinetics necessitates careful consideration of dose and therapeutic selection to reduce teratogenic risk without compromising treatment efficacy. Likewise, non-obstetric problems such as hypertension in pregnancy, gestational diabetes, auto-immune disorders and infections necessitate immediate medical intervention according to safety classifications and evolving labelling systems. Multidisciplinary care involving obstetricians, pharmacists, subspecialists and mental health professionals is crucial for managing the intricate relationships between maternal comorbidities and foetal development. Moreover, emerging domains including pharmacogenomics, placental-drug-delivery and diversity in clinical trials are further transforming the future of perinatal pharmacotherapy. This article aimed to examine the role of pharmacotherapy in high-risk pregnancies, emphasising the contemporary paradigm of safe drug use, collaboration within a multidisciplinary framework and prospective advancements to optimise maternal and foetal health outcomes. The personalised, evidence-based pharmacotherapeutic approach that improves high-risk pregnancy outcomes is based on body modifications, safe medication use, multidisciplinary approaches and advances in pharmacogenomics and placenta-targeted therapies.

Key words: High-risk pregnancy; Pharmacokinetics; Therapeutics; Obstetricians; Comorbidity.

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Citation:
Saroha G, Das R, Mehta DK. Pharmacotherapeutic strategies in high-risk pregnancy: balancing maternal and foetal safety. Scr Med. 2026 Jan-Feb;57(1):103-20.

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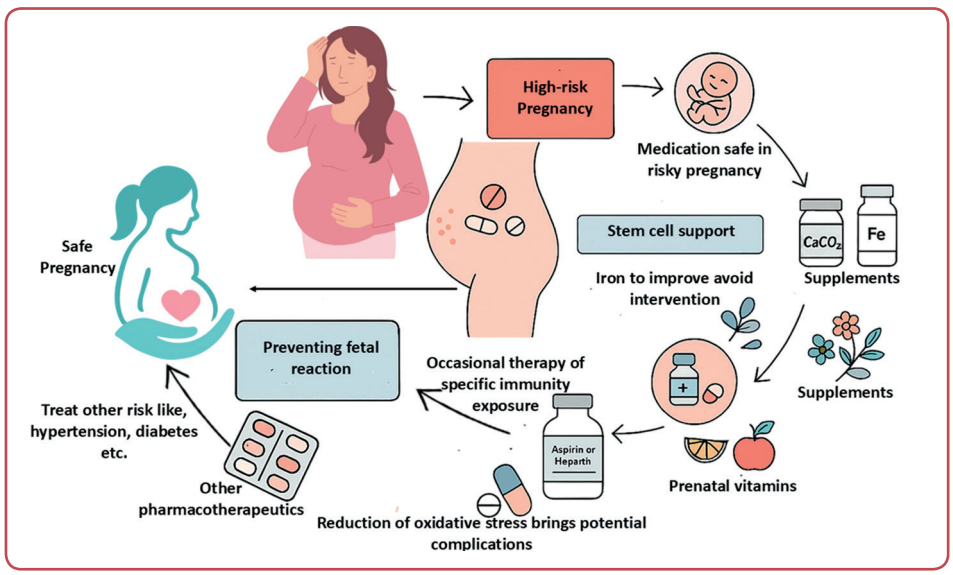
Received: 20 May 2025
Revision received: 1 August 2025
Accepted: 1 August 2025



Graphical abstract

Introduction

According to an international standard, pregnancy is "High-risk when the mother, foetus or newborn has an unusual risk of morbidity or mortality either before, during or following delivery".[1-3] This risk increases with maternal age, extremes of 17-35 years, comorbidities like diabetes, hypertension and thyroid illnesses, multiple gestations, personal history of pregnancy-related risks, genetic susceptibility and lifestyle choices like smoking and substance use.[4] High-risk pregnancies require close monitoring, specialist treatment and a strong medical and interdisciplinary team to reduce problems.[1]

Perinatal causes kill around 800 mothers daily and high-risk pregnancy affects 20 million people worldwide.[5] A study in India found that 49.4 % of pregnant women had high-risk pregnancies, with 33 % having one and 16.4 % having two or more.[6] Short birth spacing, unfavourable birth outcomes, lack of education and low socioeconomic position are common causes.[6] A second study revealed 29 % of women at high risk, with hypothyroidism (9.6 %), pregnancy-induced hypertension (6.5 %) and severe anaemia (3.2 %) being the most common diseases.[7] Gestational-diabetes, twin-gestation, oligohydramnios and Rh-incompatibility are also significant among the high-risk factors.[7, 8]

The diagnosis and treatment of high-risk pregnancies include preconception and prenatal screenings, assessment of modifiable and non-modifiable risk factors and regular prenatal visits, laboratory tests and imaging. Enhancing chronic illness management, genetic counselling, dietary support and lifestyle risk modification are intervention strategies. Quality communication, couple education and shared decision making should improve maternal and foetal outcomes while avoiding unnecessary interventions. "If managed properly and timely, a high-risk pregnancy can yield healthy outcomes for mother and child".[9]

Sleep deprivation during pregnancy, often owing to work and family duties, is linked to systemic inflammation and poor mother and newborn outcomes. Sleep quality has also been associated to preterm birth, hypertension, caesarean delivery, stillbirth, neonatal intensive care unit (NICU) hospitalisation and low Apgar scores. Sleep problems also raise the risk of postpartum depression and can affect foetal growth and survival, emphasising the importance of sleep health during pregnancy.[10, 11] Impact of sleep deprivation on maternal and foetal outcomes shown in Figure 1.

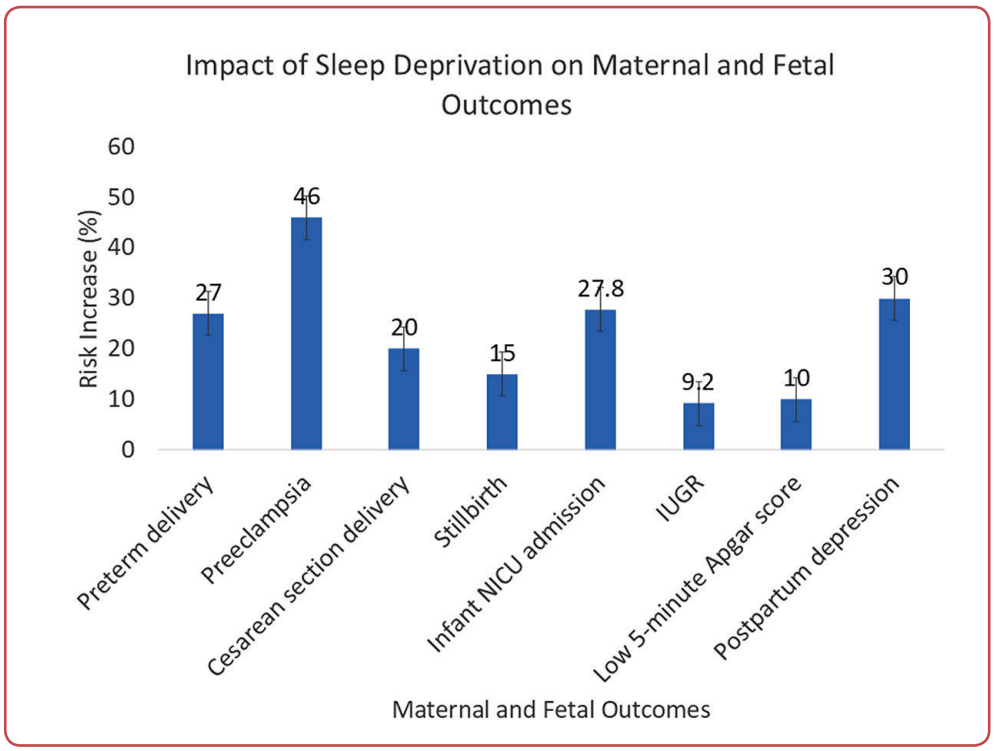


Figure 1: The impact of sleep deprivation during pregnancy

NICU: neonatal intensive care unit; IUGR: intrauterine growth restriction;

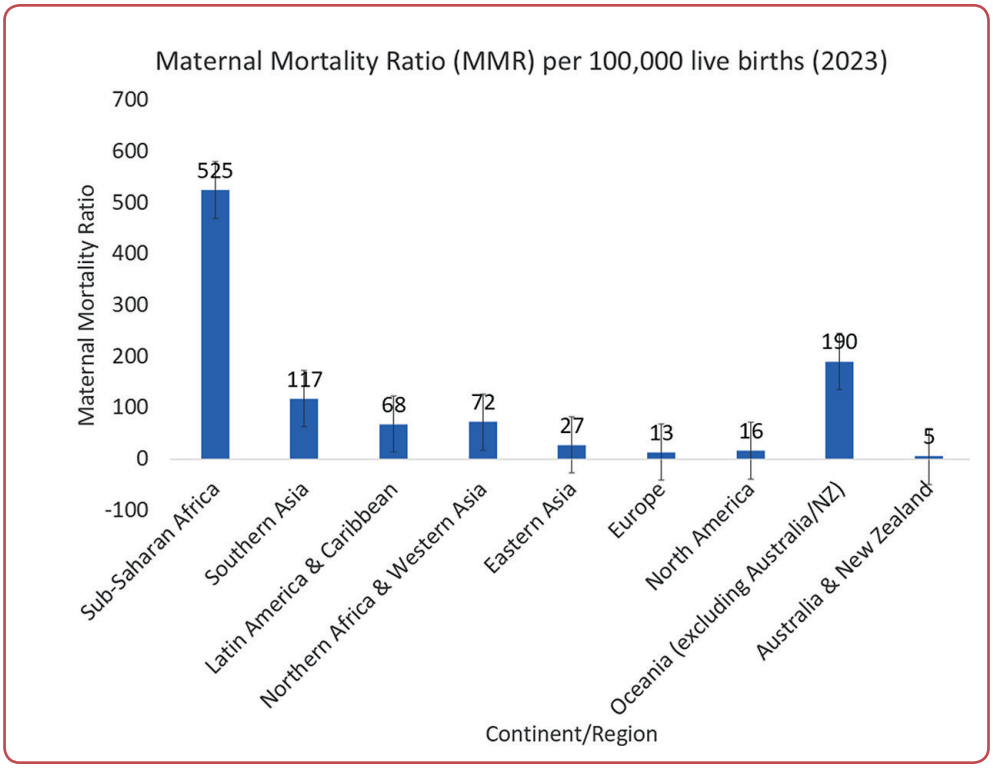


Figure 2: Maternal mortality according to different region in 2023. According to UNICEF and WHO, maternal death ratio is decrease but not nil. Ratio is highest in Sub-Saharan Africa and lowest in Australia and New Zealand

At 500 per 100,000 live births, Sub-Saharan Africa has the highest maternal mortality ratio (MMR) worldwide (Figure 2). Central and Southern Asia have improved to 110 MMR, while the Americas average 59, with substantial country-level heterogeneity. High-income countries like Europe, Australia and New Zealand have MMRs of 5-10, while Eastern Europe has the largest rate decline of 75 % since 2000. North America shows a little rising trend, with the US at 21 MMR. The 2030 SDG goal of an MMR below 70 is still difficult, especially for low-income nations.[12-14]

Pharmacotherapy treats hypertension, infections and pain to protect the mother and foetus during pregnancy. Due to prenatal danger and physiological changes, drug choice and dosage must be carefully considered.[15, 16] Calcium channel (CC) blockers and beta-blockers are used to lower maternal blood pressure without harming foetuses. Some analgesics and antiepileptics can cause birth abnormalities or developmental difficulties, so use cautiously. Successful pregnancy pharmacotherapy relies on tailored, evidence-based strategies to optimise maternal benefit/foetal safety.[17]

Understanding drug use in pregnancy

Pregnancy drastically alters many physiological processes that affect drug absorption, distribution, metabolism and excretion, which must be considered in drug dose and therapy management (Figure 3). Gastrointestinal (GI) motility and stomach emptying slow during pregnancy due to hormonal changes and the growing uterus. This delay can slow drug absorption, but not its magnitude and impact the start of effect for orally delivered pharmaceuticals.[18-20]

The body's fluids and extracellular fluids increase with plasma volume growth of 30-50 %. This "dilutes" plasma medication concentrations, especially hydrophilic medicines. Plasma albumin concentration may decrease, reducing protein binding and increasing the free (active) percentage of highly protein-bound medicines. Pregnancy may increase adipose tissue, which may impact lipophilic medication distribution. These alterations affect tissue partitioning and drug plasma concentrations.[20, 21] Additionally,

liver metabolism is complicated and imbalanced. CYP3A4 and CYP2D6 inducers improve drug metabolism and clearance. Low-activity enzymes such CYP1A2 or CYP2C19 may inhibit caffeine metabolism. Other phase II enzymes and UGT are also more active. The last outcome is pathway-specific.[21] When renal flow and GFR rise 30–50 %, the kidneys clear lithium and digoxin more effectively. It would also boost tubular reabsorption. To keep therapeutic drug levels, it calls for regular dose changes.[21, 22]

The placental barrier separates maternal and foetal blood, filtering gasses, nutrients, waste and medications. It consists of syncytiotrophoblast, cytotrophoblast, connective tissue and foetal capillary endothelium, forming a transport and selection barrier for various substances. Proper foetal development requires this, but it also affects foetus exposure to medications and xenobiotics consumed by the mother.[23, 24]

Several ways allow drugs to pass the placental barrier (Figure 4). Passive diffusion is the most common transmembrane transport method for tiny, lipophilic, non-ionised molecules under 500-600 Da (Dalton).[25, 26] Passive diffusion depends on drug lipophilicity, ionisation, size of molecules, concentration gradient, placental thickness and surface area. Plasma-protein-binding in the mother and foetus and maternal blood flow to the placenta affect transfer.[24, 26] The placenta easily transports medications like lidocaine and warfarin via passive diffusion.[24]

Active transport and facilitated diffusion are also involved in the transport of hydrophilic or low-permeability substances across membranes, in addition to passive diffusion. Facilitated diffusion necessitates no energy expenditure and employs carrier proteins to assist the substance in moving down a concentration gradient, whereas active transport utilises energy (ATP) to trans-

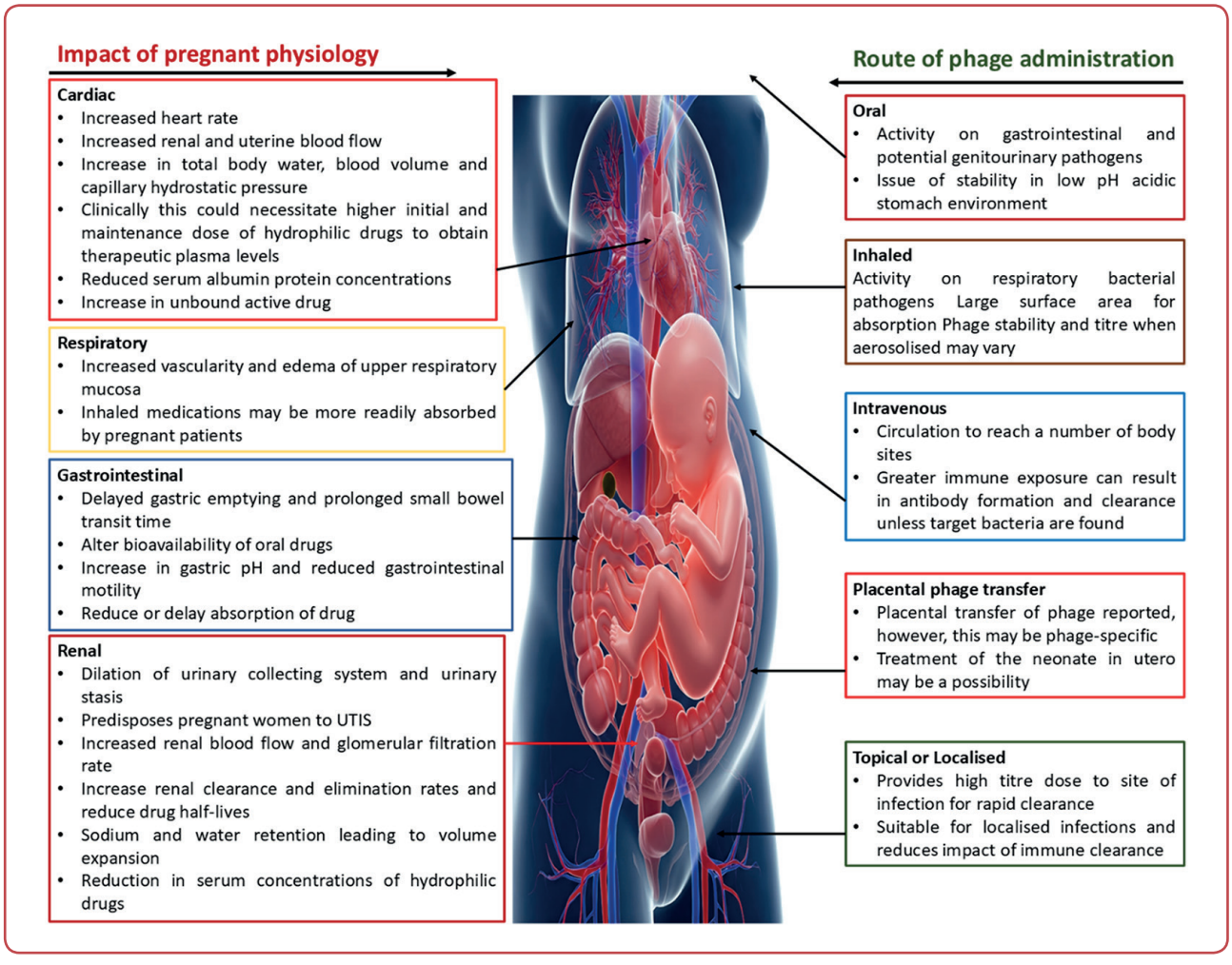


Figure 3: Different physiological changes and route of drug administration of drug. Effects on pharmacokinetic parameters of drug (ADME)

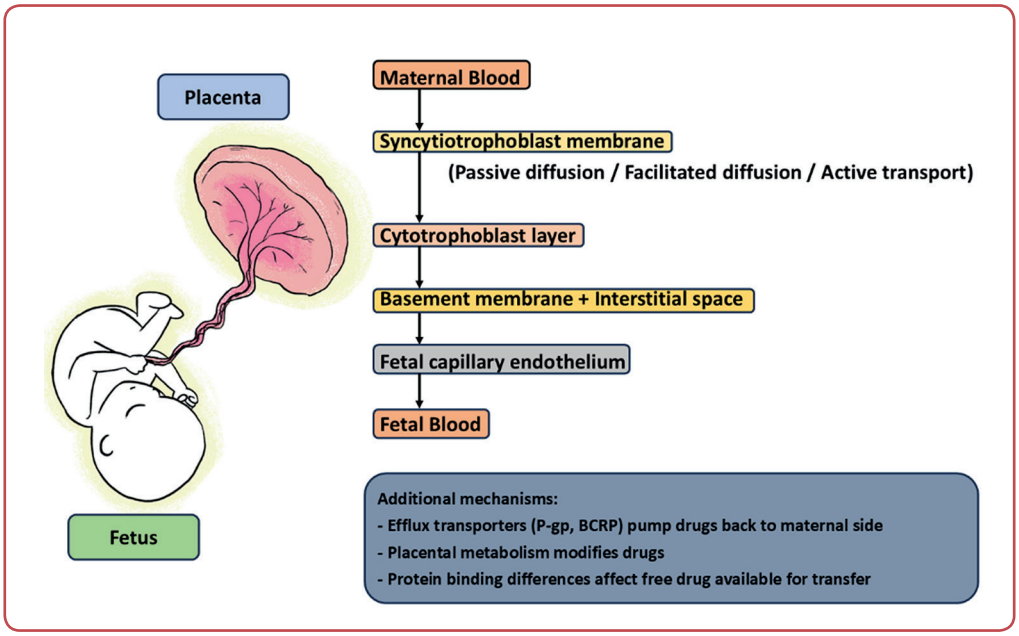


Figure 4: Mechanism of drug penetration from placenta to foetus of drug (ADME)

port pharmaceuticals against a concentration gradient.[23, 24] The placenta expresses a variety of transporters, including those from the "solute carrier (SLC) and ATP-binding cassette (ABC)" superfamilies: "P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and multidrug resistance-associated proteins (MRPs)".[24, 25] They may enhance foetal drug uptake or efflux medicines back into maternal circulation, safeguarding the foetus from hazardous toxins.[25] For instance, P-gp limits foetal access to dexamethasone and certain antiretrovirals.[24, 25] Endo-cytosis and trans-cytosis also happen but are more significant for bigger molecules and proteins than placental drug transfer.[23, 25] Drug transfer capacity and directionality can also be affected by placental architecture, transporter expression and pathological states like pre-eclampsia (Table 1).[25, 26]

Drug classification schemes help clinicians and patients make prenatal medication safety decisions, but they all have pros and cons (Table 2). Most famous is the previous "U.S. Food and Drug Administration" (FDA) pregnancy risk category system, which categorised drugs as A, B, C, D, or X based on animal and human teratogenic risk. Controlled trials showed no risk for category A medicines, but category X drugs had an evident pregnancy risk due to positive foetal damage. Categories B, C and D included increasing uncertainty or danger accompanying probable mother benefit.[30-32]

Table 1: Different mechanism of drug crossing via placenta

Mechanism	Description	Examples / features
Simple passive diffusion	Moving tiny, lipophilic, non-ionised medicines along membrane concentration gradients.	Molecular dimensions, lipid the solubility of and concentration gradient determine most common.[27, 28]
Facilitated diffusion	Energy-free carrier-mediated concentration gradient transport.	Transporters of glucose and amino acids.[27]
Active transport	Protein-mediated energy-dependent transport versus concentration gradient.	Efflux transporters like P-gp, BCRP; uptake transporters.[22, 27, 29]
Endocytosis / pinocytosis	Vesicle-mediated large-molecule or complex uptake.	Rare; may transport immunoglobulins or big peptides.[29]
Para-cellular transport	Cell junctions restrict movement due to stiff barriers.	Pathological conditions may increase; usually minor.[29]

Table 2: Different drug classification category in pregnancy

Classification system	Description	Strengths	Limitations
FDA pregnancy categories (old system)	Animal and human data-based alphabetical medication foetal risk categories.	Simple, well-known, communicable.	Too basic; lacks risk/benefit information; misinterpreted categories; stopped in 2015.
Since 2015, FDA PLLR	Risk summaries, clinical concerns and statistics are provided by narrative labelling instead of letter categories.	Nuanced, comprehensive, promotes informed decision-making.	More complicated; physicians must interpret; less intuitive than letter classifications.
Anatomical therapeutic chemical (ATC) classification	Hierarchical medication classification by anatomical place and therapeutic/pharmacological qualities (5 levels).	Worldwide standard; useful for the field of epidemiology research and drug use.	Lacks safety and risk information; often indication-specific; complicated hierarchy.
USP drug classification system (USP DC)	Chemical and therapeutic USP category granular classification.	Detailed, supports safety and quality standards.	Designed for regulating and compendial usage, not clinical risk assessment.
DEA/EUDA controlled substance schedules	Schedule I-V: abuse and medical use classification.	Controls drug usage and abuse.	Considering abuse potential rather than therapeutic classification or pregnancy safety.
Drug classes by mechanism or therapeutic use	Classifying pharmaceuticals by chemical or therapeutic usage.	Medically intuitive; helpful in prescribing and instruction.	Unstandardised classification criteria; little regulatory guidance.

FDA: Food and Drug Administration US; PLLR: Pregnancy and Lactation Labeling Rule; DEA: US Drug enforcement Administration; EUDA: The European Union Drugs Agency;

There was also tremendous pushback against the FDA letter-category system. First, it oversimplified complex risk information, producing the false impression of a linear risk progression and neglecting drug risk differences within a category. Second, it ignored exposure time, dose and data quality and often combined medicines with very different risk profiles. This produced confusion and sometimes incorrect clinical judgments because letters were given to medications with various safety profiles.[33, 34]

The "Pregnancy and Lactation Labeling Rule" (PLLR) replaced letter categories in 2015 to address these constraints. Unlike its predecessor, the PLLR employs narrative approaches to portray clinical issues, pregnancy, lactation, reproductive hazards and related statistics. This approach offers actionable information for patients and doctors, risk summaries, evidence-based pregnancy registries and actionable information. By progressively disconnecting advice from predefined structure to fit to new knowledge, the PLLR stresses individual decision making above scheduled "data-dropped pointer" grade computations.[32, 35]

The PLLR system has issues too. Clinical practitioners must examine extended narratives instead of using short references due to their intricacy. This is particularly challenging in fast-paced clinical settings or for practitioners without teratology and medication safety expertise. Australia uses ADEC and Sweden uses FASS, hence there are international inconsistencies. Studies reveal that different systems classify the same medicine differently, making global drug safety communication challenging.[33, 34, 36]

Common high-risk conditions requiring pharmacotherapy

Preventive pharmacotherapy

Folic acid administration in prenatal vitamins is a classic example of preventative medication (Figure 5). Folate, a B-vitamin, is essential for cell division and DNA synthesis. Folic acid before conception and during early pregnancy has been shown to reduce the risk of NTDs including *spina bifida* and anencephaly. The CDC urges all

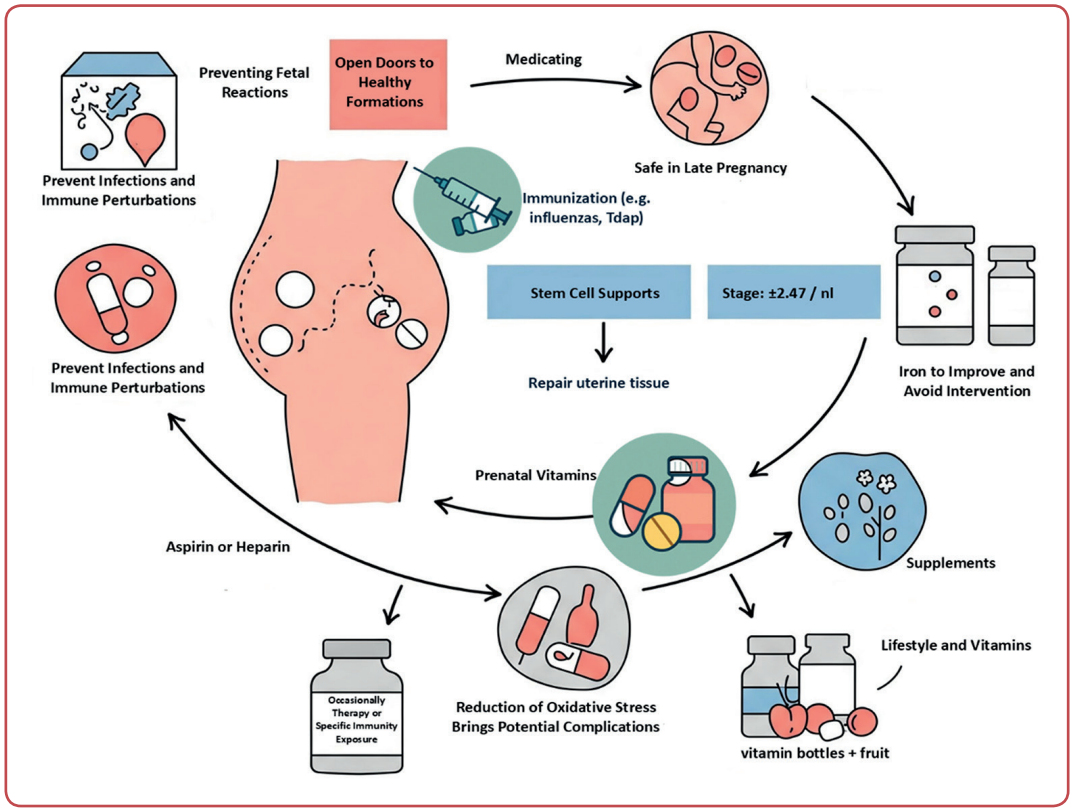


Figure 5: Preventive pharmacotherapy in pregnancy. Immunisation, different vitamin, folic acids, iron etc have a good impact on prevention of high-risk pregnancy.

reproductive women to take 400 micrograms of folic acid daily for prevention. However, this approach complicates worldwide drug safety communication.[36, 37] Prenatal vitamins contain iron, calcium and other minerals essential for mother and foetal health.[38, 39] Anaemia, bone health and PreE risk reduction are the goals of these supplements. Prenatal vitamins and folic acid ingestion is a simple, effective way to improve pregnancy outcomes worldwide.[40-42]

Pregnancy immunisations protect mother and child from major infectious illnesses.[43, 44] The CDC strongly recommends flu, Tdap, COVID-19 and RSV immunisations during pregnancy.[43, 44] When administered properly, these vaccinations minimise the chance of maternal sickness and bad pregnancy outcomes and provide passive protection to newborns during the early months of life, when they are most vulnerable.[45, 46]

Due to the risk of hospitalisation, premature delivery and foetal distress, pregnant women must receive the flu vaccine annually. The safe deactivated flu vaccine protects mother and child from flu-related illness.[43] All 27–36-week pregnancies should get the Tdap immunisation. The foetus receives the highest pertussis ("whooping cough") antibody during this time, protecting unvaccinated neonates.[43, 47] Recent recommendations indicate *Pfiser's Abrysvo* RSV vaccination for pregnant women between 32- and 36-weeks' gestation during RSV season (usually September to January in the US) to avoid serious RSV infection in newborns under six months old. This maternal immunisation regimen reduces neonatal RSV-associated infections in the respiratory system.[48, 49] Pregnant women should also get vaccinated against COVID-19 to lower the possibility of severe sickness, preterm birth and other consequences. COVID-19 vaccinations are secure and efficient during pregnancy and protect neonates.[50] Due to foetal dangers, live attenuated vaccines like MMR, varicella and LAIV are contraindicated during pregnancy. Vaccination before conception or postpartum is advised.[51] Given individual exposure risk, hepatitis A and B, meningococcal and travel-related immunisations may be given if the benefits outweigh the dangers.[51]

Common pharmacotherapy required high-risk conditions

Hypertensive disorders

Hypertensive disorders of pregnancy (HDP) impact 13 % to 15 % of US pregnancies and 15 % of reproductive-age women worldwide.[52] The spectrum of HDP includes preeclampsia (hypertension with proteinuria or organ dysfunction), eclampsia (preeclampsia with seizures), gestational hypertension (new-onset hypertension after 20 weeks without proteinuria), chronic hypertension (present before pregnancy or diagnosed before 20 weeks› gestation) and HELLP syndrome (a severe form involving haemolysis, elevated liver enzymes and low platelets) (Figure 6).[52, 53] Between 2007 and 2018, chronic hypertension nearly doubled, while overall HDP in the US rose from 2.7 9% in 1989 to 8.22 % in 2020.[54, 55]

Advanced maternal age, obesity, pre-existing hypertension, diabetes and racial/ethnic inequalities are HDP risk factors and historically deprived populations had higher prevalence and worse outcomes.[53, 54] HDP considerably increase the risk of placental abruption, acute renal failure, pulmonary oedema, stroke and eclampsia or HELLP syndrome. Foetal risks include preterm birth, intrauterine growth restriction (IUGR), low birth weight, stillbirth and neonatal morbidity and mortality.[52] Untreated or severe hypertension in pregnancy causes placenta hypo-perfusion, therefore restricting foetal growth and raising newborn death.[54]

To prevent serious outcomes, HDP care places a strong emphasis on controlling maternal blood pressure and preserving uteroplacental perfusion. According to current guidelines, antihypertensive medication should be started as soon as blood pressure exceeds 140/90 mmHg and serious cases of hypertension (≥ 160/110 mm Hg) should be treated right away.[52] Antihypertensives such labetalol, nifedipine and methyldopa are advised for pregnant women due to their safety.[53] Magnesium sulphate is the standard of excellence for preeclampsia seizure prevention and treatment.[52] Recent CHAP trial studies indicate that treatment even mild chronic high blood pressure during pregnancy helps to prevent serious preeclampsia, abruption of placenta and preterm birth without increasing low birth weight.[54] Regular observation of mother›s and foetal condition helps to determine birth timing to strike a risk balance.

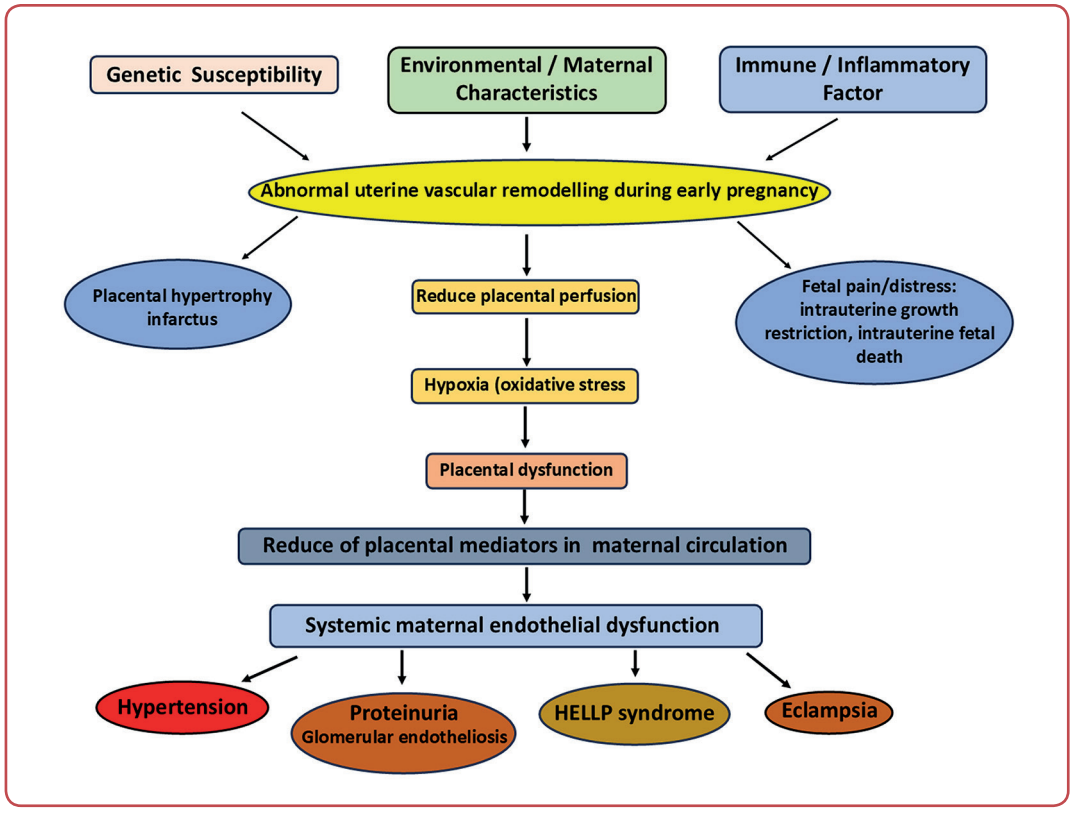


Figure 6: Pathophysiological mechanism of hypertension in pregnancy

Table 3: Different type of hypertension during pregnancy

Classification system	Description	Key features / diagnostic criteria	Prevalence / impact	Reference
Chronic Hypertension	High blood pressure before pregnancy or detected before 20 weeks.	BP ≥ 140/90 mm Hg before pregnancy or 20 weeks; may coincide with preeclampsia.	In ~1-5 % of pregnancies, it raises the risk of preeclampsia and severe consequences.	[60]
Gestational Hypertension	New-onset hypertension after 20 weeks no proteinuria or end-organ damage.	No proteinuria or systemic symptoms; BP ≥ 140/90 mm Hg after 20 weeks.	Occurs in 6-17 % of pregnancies; a risk factor for preeclampsia and preterm birth.	[60]
Preeclampsia	Post-20-week hypertension with proteinuria or organ impairment.	BP ≥ 140/90 mm Hg in combination with proteinuria (≥ 300 mg/24 h), thrombocytopenia, renal/liver dysfunction, or cerebral.	This occurs in ~4-5 % of pregnancies and is a major factor in maternal/foetal mortality.	[61]
Eclampsia	Uncaused seizures in preeclampsia patients.	Preeclampsia seizures; medical emergency.	Low prevalence (~0.1–0.3 %); significant risk of maternal/foetal death without treatment.	[60]
HELLP Syndrome	Severe preeclampsia with haemolysis, increased liver enzymes and low platelets.	AST/ALT increase, haemolysis, platelet count < 100,000/μL.	Only 0.1–0.6 % of pregnancies have life-threatening complications such liver rupture and stroke.	[60]

Methyldopa, labetalol and long-acting nifedipine are recommended for persistent hypertension in pregnancy due to their safety. For chronic management and acute severity, labetalol and nifedipine are also utilised, but methyldopa is usually the primary choice, especially during pregnancy[56, 57] and hypertension episodes.[57, 58] Usually, hydralazine is administered intravenously for acute severe hypertension crises. Because of teratogenicity, «angiotensin receptor blockers (ARBs)» and «angiotensin-converting enzyme inhibitors (ACE inhibitors)» are banned in pregnancy.[56, 57]

Pregnant women with high blood pressure (BP) (> 160/110 mm Hg), proteinuria and headaches or vision issues after 20 weeks show clear preeclampsia. HELLP syndrome progression may be indicated by increased liver enzymes and thrombocytopenia. Magnesium sulphate for seizure prophylaxis and labetalol for hypertension must be started. Foetal monitoring often demonstrates placental insufficiency-induced growth limitation. To avoid complications, delivery planning often balances mother stabilisation and foetal development, producing preterm birth (Table 3).[54, 55, 59]

Diabetes mellitus in pregnancy

Due to its potential impact on mother and foetal health, pregnancy with diabetes mellitus, including pregestational diabetes and GDM, presents unique challenges.[62, 63] GDM results from pancreatic function failing to overcome insulin resistance brought on during pregnancy.[64] Placental hormones such lactogen, oestrogen, progesterone and cortisol cause insulin resistance, ensuring the foetus gets enough glucose. GDM women develop hyperglycaemia because their pancreas cannot compensate for insulin resistance.[65] For best results, pregestational diabetes—pre-existing type 1 or type 2 diabetes—requires careful pregnancy treatment.[66]

The main goal is to get and keep optimal glycaemic control to reduce the risk of mother's and foetal complications.[67] Insulin's effectiveness and absence of placental transfer make it a popular GDM treatment. Insulin is preferred for GDM control due to its effectiveness and lack of placental transfer. Intermediate-acting insulin (NPH) can be taken at night, however lispro and aspart can be given before meals.[66] Self-monitoring of blood glucose (SMBG) results drive insulin dosage modification. Metformin and glyburide can replace insulin. Metformin crosses the placenta despite its safety. Glyburide increases newborn hypoglycaemia risk more than insulin and metformin.[68] Oral medicine policies vary; some recommend insulin first.[66] SMBG is vital for glucose monitoring and medication adjustments. Ultrasound and antepartum testing are needed to assess foetal

well-being.[69] For continuing diabetes, postpartum tolerance to glucose testing is suggested. Type 2 diabetes risk can be reduced by lifestyle changes.[66]

Thromboembolic disorders

Since physiological changes increase risk of hypercoagulability, thromboembolic diseases—especially venous thromboembolism (VTE)—are a major concern during pregnancy. Pathophysiology is Virchow's triad—venous stasis, vascular injury and hypercoagulability. DVT requires Doppler ultrasonography, PE CTPA; diagnosis dependent on imaging. Low-molecular-weight heparin (LMWH) is the first-line treatment, but patients may choose higher dosages or twice-daily medication.[70-72]

Venous stasis, endothelial impairment and hypercoagulability enhance the risk of VTE during pregnancy.[72] Increased oestrogen, progestins and other hormonal changes during pregnancy raise coagulation factors and diminish natural anticoagulants.[73] The expanding uterus and increasing pelvic vein pressure may prevent venous return, leading to venous stagnation and increased clot formation, especially in the lower extremities.[74] Hereditary thrombophilias including factor V Leiden and prothrombin gene mutation may increase VTE risk in some women.[69, 75]

Low molecular weight heparin (LMWH) is the anticoagulant of choice for VTE in pregnancy.[76] Weight-based dosage can be administered once (higher dose) or twice a day.[76] Renal impairment, malignancy, or major weight fluctuations could be used to investigate anti-Xa levels.[75] In situations of LMWH allergy or if larger doses are required, unfractionated heparin could be taken into account.[76] Oral anticoagulants—eg rivaroxaban, apixaban are generally avoided during pregnancy because of possible placental translocation.[77]

Thrombolytics including streptokinase, alteplase etc. Set aside for life-threatening scenarios, include PE with persistent cardiovascular impairment.[75] Vena cava filters may help women who cannot be anticoagulated or have recurrent VTE.[77]

Preterm labour

A major contributor to newborn morbidity and death is preterm labour, or labour prior to 37 weeks of gestation.[78] Its complex pathophysiology includes infection, uterine overdistension and hormonal alterations.[79] Diagnosis is aided by clinical evaluation—including pelvic exams and cervical length measurements—and foetal fibronectin testing. Tocolytics delay birth; corticosteroids develop foetal lungs; and they control issues like infection.[80]

Preterm labour is said to be triggered by intrauterine infection and inflammation.[81] Too much uterine volume, especially in several pregnancies, might cause preterm labour.[78] Premature dilation and labour could result from a short cervix.[82] Changes in hormonal balance might affect uterine activity and start labour.[81] Bleeding and damage to the placenta can potentially trigger preterm labour.[58]

Tocolytics are medications that lower uterine contractions; they are used to delay delivery for up to 48 hours. Among these are beta-agonists (eg terbutaline), CC blockers (eg nifedipine) and prostaglandin inhibitors (eg indomethacin).[83] Corticosteroids, such as betamethasone or dexamethasone, are given to the mother to encourage foetal lung development and lower the likelihood of respiratory distress syndrome in preterm babies.[84] Although antenatal corticosteroids provide advantages such as increased lung maturity in preterm infants, their usage in pregnancy has drawbacks and possible hazards. These include potentially low blood sugar in babies, possibility for smaller birth weight with repeat doses and a possible association between steroids and lower academic achievement later in life. There is also growing worry about possible damage under non-standard circumstances, such elective caesarean procedures at term, when corticosteroids are administered.[85, 86] Used as a neuro-protectant for preterm newborns, especially those born at 24-32 weeks' gestation, magnesium sulphate.[87] Antibiotics could be recommended to prevent or manage intrauterine infection if one suspects infection.[82]

Bacterial, viral and fungal infections

During pregnancy, bacterial, viral and fungal illnesses require cautious management, typically medication. Many antibiotics and antivirals are safe during pregnancy, while some may harm the foetus. Fungal infections may require oral or topical antifungals for prenatal safety.[88-90]

Though vaginal clindamycin cream is not advised in the third or fourth trimester, Metronidazole or clindamycin (oral or vaginal) are suggested in bacterial vaginosis (BV).[91] Azithromycin and ceftriaxone are used to treat *Chlamydia* and *Gonorrhea*, with ceftriaxone being preferred.[88, 92] Penicillin or clindamycin intrapartum antibiotic prophylaxis is essential to prevent neonatal infections.[93] Penicillins, cephalosporins and nitrofurantoin are used for UTIs, however fluoroquinolones and tetracyclines should be avoided.[88] For *Listeria*, ampicillin and/or erythromycin are administered, although their safety during pregnancy should be assessed.[94]

Acyclovir, valacyclovir and famciclovir reduce viral shedding and prevent HSV outbreaks, although its safety during pregnancy is unknown.[89] Varicella-Zoster virus (VZV) infection is treated using acyclovir and VZV immunoglobulin; acyclovir is preferred.[90] Includes surveillance and antiviral medication for Hepatitis B and C infection; some drugs' safety during pregnancy is unknown.[95] Antiretroviral therapy is essential for maternal health and preventing foetal transmission in HIV/AIDS patients, hence close monitoring and care are needed.[96]

In treatment of vulvovaginal candidiasis (VVC), topical azole antifungals are first-line, with oral fluconazole considered as a second-line option.[97, 98] Amphotericin B (liposomal) is often utilised in the first the first trimester for the management of systemic fungal infections because of teratogenic concerns with azole antifungals.[89]

Autoimmune disorders

Pharmacotherapy for autoimmune diseases during pregnancy aims to control disease activity and reduce foetal hazards. Often, this calls for a multi-disciplinary team including rheumatologists and obstetricians. While corticosteroids and immune-suppressants could be explored for other diseases such immune thrombocytopenia, medications such low-dose aspirin and anticoagulants could help manage antiphospholipid syndrome. Many doctors also recommend hydroxychloroquine for diseases including systemic lupus erythematosus.[99, 100]

Antiphospholipid syndrome, blood clotting and the risk of problems like preeclampsia and foetal death are usually managed with low-dose aspirin and anticoagulants.[99] Flare-ups of immune thrombocytopenia (ITP) may be controlled by corticosteroids such as prednisone or methylprednisolone. One might also think about immunosuppressants such as azathioprine.[101] Hydroxychloroquine is usually started or sustained during pregnancy to treat systemic lupus erythematosus (SLE), therefore controlling disease activity and enhancing pregnancy results. Especially in the second and third trimesters, flares may be controlled using corticosteroids.[102-104] In case of rheumatoid arthritis, corticosteroids may be used, but the decision to continue or discontinue other medications (like TNF inhibitors or DMARDs) should be made in consultation with a rheumatologist, considering the risks and benefits for both the mother and foetus.[105, 106] In some cases, other immunosuppressants like azathioprine may be considered, but careful consideration of the risks and benefits is necessary.[107, 108]

Mental health disorders

With plasma levels falling all during pregnancy, pregnancy significantly alters the pharmacokinetics of both LTG and lithium. Common in the management of epilepsy during pregnancy, therapeutic drug monitoring of AEDs may also be beneficial in the treatment of bipolar illness during the perinatal period.[109] Brexanolone certainly helps with depression; it might raise the likelihood of somnolence or drowsiness, which would call for dose lowering or interruption. Sertraline might help with anxiety and depression symptoms as well as response and remission. Mood stabilisers might lengthen time to recurrence and lower recurrence.[110] Maternal psychological disorders throughout pregnancy have been connected to premature birth, neonatal hypoglycaemia, subpar neurodevelopmental results and impaired attachment. Among the less desirable prenatal outcomes include placental abnormalities, small-for-gestational-age foetuses, foetal pain and stillbirth.[111] Groups of psychiatric drugs contraindicated during pregnancy include valproates; others are safer, including "selective serotonin reuptake inhibitors (SSRIs)" or antipsychotics.[112]

Drug safety evaluation

Drug safety screening during pregnancy is vital because drugs can cross the placenta and harm the foetus. This examination ensures that treatment benefits outweigh foetal dangers

and highlights concerns.[113] Certain stages of foetal development, especially organogenesis (organ creation) in the embryonic phase (weeks 3-8 after conception), are most teratogenic. Clarifying this is important because teratogens are most dangerous to growing organs and systems.[114, 115] Category X drugs are well-known teratogens and are completely banned during pregnancy since they carry a high danger of significant birth defects. Among these drugs are thalidomide, warfarin, isotretinoin and many more.[116, 117] Thalidomide, an anti-emetic and anti-inflammatory, has caused thousands of neonatal limb deformities. Warfarin can cause bone and mental defects in foetuses. Isotretinoin can cause brain, heart and craniofacial abnormalities in severe acne.[117]

Registries, case-studies and post-marketing surveillance offer insights beyond clinical trials. Thus, real-world therapeutic efficacy and safety are better understood. The only ways to collect and analyse real-world data are registries, case studies and post-marketing surveillance.[118, 119]

Risk assessment and clinical decision-making

Prenatal care includes risk evaluation and clinical decision-making, especially in pregnancies with maternal or foetal problems. Doctors must consider the mother and foetus during pregnancy, which is tough. Decisions must balance medical intervention with foetal growth risks. Methodical and targeted strategies are needed to maximise maternal-foetal results and reduce damage.[113] The process of identifying potential risks to mother and foetal health, assessing their severity and hence guiding treatment decisions is called risk assessment in pregnancy. Beginning with the initial prenatal visit and running all the way through pregnancy, this approach runs. Medical (eg diabetes, hypertension), obstetric (eg history of preterm delivery), genetic, environmental, or psychosocial could all be risk factors. Doctors often categorise patients into low, moderate, or high-risk groups using standardised tools and procedures, therefore enabling early intervention and multidisciplinary care planning.[120]

Among maternal hazards are pre-existing illnesses including heart disease,[121] renal impairment,[122] auto-immune disorders.[123] and mental health issues,[124] any of which could influence the course of pregnancy and its outcome. Age (under 18 or over 35), obesity, drug use and socioeconomic position may also make pregnancy more difficult. These elements affect not only the mother's health but also the safety of medication and foetal development. Problems with maternal health can have an impact on foetal development and cause preterm delivery, low birth weight and congenital abnormalities.[121]

Multidisciplinary management

High-risk pregnancies are managed multidisciplinary by means of organised cooperation among several medical specialists guaranteeing the safety of both mother and foetus. Central to this strategy is the creation of a customised care plan developed by regular case conferences including maternal-foetal medicine professionals, neonatologists, obstetric anaesthesiologists and other pertinent subspecialists. Clearly established intervention thresholds guide risk-specific protocols—such as rigorous glycaemic monitoring for diabetic moms, echocardiographic surveillance for women with cardiac problems, or serial foetal growth scans in cases of foetal growth limitation. Essential pharmacologic measures driven by evidence-based practice are timely administration of corticosteroids for foetal lung maturity, magnesium sulphate for neuroprotection and proper use of antihypertensives or anticoagulants.[125]

Care logistics, including scheduled birth in a tertiary care institution with NICUs and 24-hour multidisciplinary availability, are also critical. SBAR (situation, background, assessment, recommendation) and electronic shared records allow team members convey information consistently. Continuous labour monitoring, emergency surgical intervention planning and postpartum care team participation—especially for chronic condition follow-up—ensure long-term mother and newborn health. Audits and simulation-based training increase team readiness and patient outcomes.[126, 127]

Special populations and considerations

Managing high-risk pregnancies in distinct populations—such as women with pre-existing medical conditions, adolescent mothers, advanced maternal age, or those with restricted access to healthcare—necessitates customised strategies to ensure maternal and foetal safety. Women with chronic hypertension or autoimmune disorders necessitate preconception counselling, medication adjustments and continuous monitoring to prevent complications such as preeclampsia or intrauterine growth restriction. Older pregnant women may require further testing for chromosomal abnormalities and cardiac issues, whereas adolescent mothers may benefit from emotional support, nutritional guidance and understanding of newborn care. Patients from underrepresented or underserved populations require culturally competent treatment and language-specific resources, hence emphasising the necessity of accessibility and equity in healthcare delivery. Mitigating disparities and improving prenatal outcomes across diverse communities mostly relies on the integration of social services, community health professionals and targeted outreach programs.[128, 129]

Emerging therapies and future prospective

Advancements in pharmacogenomics and tailored medicine show considerable potential for improving results in high-risk pregnancies by tailoring medications depending on personal genetic profiles. Knowing genetic variations in medication metabolic enzymes—like CYP450 isoenzymes—can help to guide prescription choices and doses, therefore lowering adverse drug reactions and optimising efficacy. For instance, pharmacogenomic testing can help change anticoagulation strategies in pregnant women with thrombophilias or tailor antiepileptic drug regimens to reduce teratogenic worries while maintaining maternal seizure control.[130] Including genetic screening into regular prenatal care might be very important in controlling complicated pregnancies with more accuracy as research in this area develops.

Innovative medication delivery techniques, such as nanoparticle-based carriers and placenta-targeted therapies, are being explored to enhance therapeutic precision and minimise systemic side effects during pregnancy. These treatments aim to deliver medications directly to maternal or foetal compartments, thereby circumventing barriers such as the placenta and reducing foetal exposure to potentially harmful substances. Liposomal formulations of corticosteroids and targeted immunotherapies are under investigation as potential therapeutics for foetal growth restriction and preeclampsia.[131] Such developments may change the management of pregnancy-specific diseases in the near future and promise a more secure therapeutic profile.

Ethical issues have traditionally kept pregnant women out of scientific studies, so depriving doctors of evidence-based information to manage high-risk pregnancies. To close this gap, nevertheless, more and more people are realising that pregnant populations should be included in biomedical research. Programs by companies like the U.S. National Institutes of Health (NIH) and regulatory changes are starting to encourage ethical involvement of pregnant women in clinical studies for vaccinations, medicines and diagnostics.[132] Generating strong, pregnancy-specific safety and efficacy data depends on this change, which will finally help to create better informed clinical decisions and fair healthcare for this group.

Conclusion

High-risk pregnancies treated with pharmacotherapy have to strike a balance between maternal and foetal health. Informed prescribing calls for knowledge of pregnant physiological changes and placental drug transfer. While vaccinations and nutrition are crucial, complicated disorders like diabetes and hypertension call for safe, expert therapies. The multidisciplinary approach handles high-risk pregnancy's medical, emotional and logistical components. Pharmacogenomics and tailored drug delivery could enhance treatment as precision medicine develops. Ethically integrating pregnant populations in clinical studies helps to fill knowledge gaps. These cooperative, scientifi-

cally motivated strategies offer more successful, fairer and safer high-risk risk pregnancy management.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

The authors wish to thank Maharishi Markandeshwar (Deemed to be) University, Mullana, India for all necessary facilities.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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