Renal Dysfunction in Pre-eclampsia: Etiology, Pathogenesis, Diagnosis and Perioperative Management: A Narrative Review

Sohel M. G. Ahmed, Layla J. M. Kily, Sikha Shastham Valappil, Shameena Ajmal, Hayat Elfil, Nada S. Elamin, and Justin C. Konje

**ABSTRACT**

Pre-eclampsia and pre-eclampsia-associated renal dysfunction (PARD) are severe morbidities during pregnancy with potentially devastating maternal and fetal outcomes. PARD has various aetiologies; understanding the physiological renal adaptation during pregnancy is paramount for early detection, diagnosis, and appropriate management to minimize maternal and fetal morbidities and mortalities. In this article, we review the current medical literature on PARD. We conducted a literature review using PubMed MEDLINE and ScienceDirect electronic databases. We accessed published work on the pathogenesis of renal dysfunction in pre-eclampsia and its management from 2005 to 2020. We aimed to highlight possible perioperative management strategies based on the pathophysiological derangements of pre-eclampsia. We used the following search terms: pre-eclampsia, renal dysfunction, pathogenesis, and perioperative management. Most of the studies we reviewed were either observational (both prospective and retrospective) or translational research studies. We also outline the primary perioperative (peri-delivery) course and discuss management options as advised by leading international societies and their challenges and considerations.

**Keywords:** Management, perioperative, pre-eclampsia, renal dysfunction.

I. INTRODUCTION

Pre-eclampsia is a multisystem disease of onset in the second half of pregnancy [1], complicating 2 to 8% of all pregnancies [2] and is one of the leading causes of maternal and perinatal morbidity and mortality globally [3]. The incidence is markedly influenced by race, ethnicity, and thus genetic predisposition. It is more common in African Americans compared to Caucasians and Hispanics. A higher incidence is seen in nulliparous compared to multiparous women [3]. The criteria for diagnosing pre-eclampsia as defined by the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence UK are shown in Table I [2], [4].
TABLE I: THE CRITERIA FOR DIAGNOSING PRE-ECLAMPSIA INCLUDE

| a) Blood pressure | • Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure or • Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. |
| b) Proteinuria | • 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio of 30mg/mmol or more or • Dipstick reading of 2+ (used only if other quantitative methods are not available) |
| c) In the absence of proteinuria, new-onset hypertension plus the new onset of any of the following is considered diagnostic of pre-eclampsia: | • Thrombocytopenia: platelet count less than 100,000 x 10^9/L • Renal insufficiency: serum creatinine concentration higher than 97.2 μmol/dL (1.1 mg/dL) or a doubling of the serum creatinine concentration in the absence of other renal diseases • Impaired liver function: elevated liver transaminases to twice the upper limit of normal • Pulmonary edema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms. |

In a systematic review by the World Health Organization (WHO), hypertensive disorders of pregnancy accounted for 16% of all maternal deaths in high-income countries (HIC), 9% of all maternal deaths in Africa and Asia and 26% in Latin America and the Caribbean [2]. One of the causes of severe morbidity and mortality is acute kidney injury (AKI). HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome and severe preeclampsia account for 38% of pregnancy-related AKI [5].

The ACOG now classifies as "pre-eclampsia with or without severe features" based on the degree of hypertension, associated biochemical derangement and clinical symptoms. Features of severity are listed in Table II. Severe preeclampsia may then progress to eclampsia or HELLP syndrome. Risk factors for preeclampsia are shown in Table III. The strongest predictor for developing pregnancy-related AKI is a previous pregnancy history complicated by hypertension [6].

Pre-eclampsia is the leading cause of nephrotic syndrome during pregnancy [7]. The glomerular filtration rate (GFR) increases by 40 to 60 % in a normal pregnancy. In pre-eclampsia, there is a significant decrease in both GFR and renal plasma flow by 30 to 40% [7]. Proteinuria in pre-eclampsia reflects the loss of both size and charge selectivity of the glomerular barrier, which is regained 3 to 8 weeks post-delivery. Rarely it can persist for months postpartum. Elevated serum uric acid levels in pre-eclampsia result from decreased renal clearance rather than tissue breakdown from hypoxia [7]. Rarely, acute tubular necrosis can occur with severe preeclampsia due to prolonged renal hyperperfusion.

TABLE II: SUMMARY OF SEVERE FEATURES OF PREECLAMPSIA

<table>
<thead>
<tr>
<th>Severe features in Preeclampsia</th>
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<tbody>
<tr>
<td>1. Systolic blood pressure of 160 mm Hg or more and/or diastolic blood pressure of 110 mm Hg or more on 2 occasions at least 4 hours apart (unless antihypertensive therapy has been initiated before this time)</td>
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<tr>
<td>2. Thrombocytopenia (platelet count less than 100,000 x 10^9/L)</td>
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<tr>
<td>3. Impaired liver function as indicated by abnormally elevated blood concentration of liver enzymes (twice the upper limit of normal)</td>
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<td>4. Severe persistent right upper quadrant pain or epigastric pain not responding to medication, and other alternative causes ruled out.</td>
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<tr>
<td>5. Renal insufficiency (serum creatinine concentration more than 1.1mg/dl or doubling of the serum creatinine concentration in the absence of other renal diseases)</td>
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<tr>
<td>6. Pulmonary edema</td>
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<tr>
<td>7. New onset headache unresponsive to medication and not accounted for by alternative diagnosis</td>
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<tr>
<td>8. Visual disturbances</td>
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TABLE III: RISK FACTORS FOR DEVELOPING PRE-ECLAMPSIA

<table>
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<tr>
<th>Women at high risk</th>
<th>Women at moderate risk</th>
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<tr>
<td>• Hypertensive disease during a previous pregnancy</td>
<td>• First pregnancy age 40 years or older</td>
</tr>
<tr>
<td>• Chronic kidney disease</td>
<td>• Pregnancy interval of more than ten years</td>
</tr>
<tr>
<td>• Autoimmune diseases such as systemic lupus erythematosus or antiphospholipid syndrome</td>
<td>• BMI of 35 kg/m2 or more at the first visit</td>
</tr>
<tr>
<td>• Type 1 or type 2 diabetes</td>
<td>• Family history of Pre-eclampsia</td>
</tr>
<tr>
<td>• Chronic hypertension</td>
<td>• Multiple pregnancies</td>
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II. METHODOLOGY

A thorough and comprehensive literature search in medical databases (PubMed MEDLINE and ScienceDirect electronic databases) was performed with stepwise changes in relevant keywords (pregnancy, pre-eclampsia, renal dysfunction, perioperative management). Search was restricted to manuscripts written in English, including case reports, observational studies, randomized controlled trials (RCTs), translational research, academic societies guidelines and review articles.

III. PATHOGENESIS OF PRE-ECLAMPSIA

The exact cause of pre-eclampsia is unknown, but several mechanisms have been proposed, including fetal and maternal genetic factors, biochemical, immunological, angiogenic and anti-angiogenic factors [8]. Some of these also play an essential role in the development of cardiovascular, cerebrovascular, or permanent renal dysfunction later in life [9].

Spiral arteries remodeling in early pregnancy is essential for adaptive blood flow and efficient nutrient and gas exchange with the developing fetus. In patients who develop preeclampsia, these spiral arteries are defective and incomplete [10]-[12]. Abnormal trophoblastic invasion combined with pathological decidual adhesion molecules is
thought to be responsible for this [10]. The decidual uterine natural killer (uNK) cells fail to chemo-attract trophoblasts to the spiral arteries. Other immune cells, such as T-helper cells, undergo unbalanced differentiation, and a combination of the pro-inflammatory cytokines, immune mediators and placental growth factor disrupts contributes to a cytotoxic environment in the uterine bed [13]. Therefore, spiral arteries remain narrower within the uterine bed [10], [14]. These narrow spiral arteries lead to reduced perfusion, resulting in a localised hypoxic-ischaemic environment leading to a state of placental stress (Fig. 1).

Various mediators are then produced and released into the circulation, where they cause systemic vascular dysfunction and endothelial cell (EC) damage [10]. These changes start early (late first trimester) and progressively become more severe; hence patients may remain subclinical and only manifest symptoms later during the pregnancy. Fig. 2 summarises the pathological steps and implicated mediators in the pathogenesis of preeclampsia.

IV. ALTERED RENAL FUNCTION IN PREECLAMPSIA

The kidneys undergo remarkable changes as part of the normal physiological adaptation to pregnancy. The effective plasma flow rate increases by up to 80%, and the GFR increases by 40-60% compared to the non-pregnant state [8]. In preeclampsia, however, the GFR decreases as the disease progresses due to EC damage of the glomerulus from the hypoxia-induced stress mediators of the developing placenta [10]. There is also increased protein loss due to the result of the oxidative stress associated with placental ischaemia [10]. Nitric Oxide (NO) production is reduced through suppression of the NO synthetase enzyme via sFLT-1VEGF and sEng-Transforming Growth Factor-β (TGF-β) pathways [10]. In an animal study, [18] found that administration of sFlt1 to pregnant rats in their second trimester induced hypertension, proteinuria, and glomerular endotheliosis, the classic lesion of pre-eclampsia.

V. PREECLAMPSIA INDUCED GLOMERULOPATHY

The anti-angiogenic mediators released from the ischaemic placenta in women with pre-eclampsia affect the kidney as part of the disease process, causing deterioration in kidney function before proteinuria [10]. This pathological process is said to predate the onset of symptoms by weeks.

In addition to the mediators summarized in Fig. 2, there is EC injury, inflammation, and vasoconstriction, which lead to the hypertension seen in pre-eclampsia; placental soluble fms-like tyrosine kinase-1 (sFLT-1) and soluble Endoglin (sEng) antagonise the effects of podocyte vascular endothelial growth factor (VEGF) on the renal ECs. The autocrine VEGF, and paracrine function of VEGF acting through the glomerular basement membrane, are also antagonized. The result of this is a disruption in the standard regulatory mechanisms that maintain the integrity of the glomerulus. Additionally, glomeruli undergo further cellular injury due to the increased production of reactive oxygen species (ROS) due to the oxidative stress associated with placental ischaemia [10].

![Fig. 1. Spiral artery and trophoblastic invasion seen in a normal pregnancy (A) compared to the defective spiral artery remodeling in preeclampsia (B).](Image)

In preeclampsia there is less trophoblastic invasion of the myometrium. The spiral artery remodeling is defective and incomplete leading to shallower and narrower spiral arteries with impaired blood flow (B). This causes a localized hypoxic-ischaemic environment causing placental stress which then develops into the preeclampsia maternal syndrome.

![Fig. 2. Pathogenesis and mediators implicated in preeclampsia. From blastocyst implantation until the maternal syndrome seen in preeclampsia.](Image)

(Abbreviations: Ang-II: Angiotensin-II; AT1-AA: Angiotensin 1 autoantibodies; BBB: Blood brain barrier; C1q: Complement 1q; ET-1: Endothelin-1; HELLP: Haemolysis elevated liver enzymes and low platelets; HLAC2: Histocompatibility Antigen Complex C2 group; IL: Interleukin; KIR AA: Killer immunoglobulin receptor AA genotype; LFT: Liver function test; NO: Nitric oxide; PAI-1: 4G/5G: Plasminogen Activator Inhibitor type 1 gene; PG2: Prostaglandin-2; ROS: Reactive oxygen species; sENG: soluble endoglin; sFLT-1: soluble fms-like tyrosine kinase-1; STBM: syncytiotrophoblast microparticles; TGF-β: Transforming growth factor β.)

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Glomerular endotheliosis, a term used to describe the microscopic glomerular appearance, is not limited to renal pathology in pre-eclampsia [18]. The appearance is a variation of thrombotic microangiopathy where the glomerular endothelial cells are swollen along with fenestrae and capillary lumen occlusion [10], [19]. The degree of endotheliosis varies between each glomerulus. This can be attributed to the increased vasoconstriction caused by released endothelin-1 (ET-1) and concomitant reduction in the production of the vasodilators NO and prosstaglandin-2 (PG2).

Overexpression of tissue factor within the uterine decidua and placenta contributes to the pro-coagulant state of pregnancy. Pre-eclampsia worsens this state as ECs produce less NO and PG2. Additionally, platelets are larger and activated by increased thromboxane A2 (TXA2) produced by these damaged ECs. This contributes to vessel occlusion by thrombosis as well as fibrin deposition [10], further propagating renal injury in preeclampsia.

The glomerular wall comprises three layers; ECs, a basement membrane formed from proteoglycans and mesangial cells and charge selective slit diaphragms formed by podocytes [10], [20]. The glomerular ECs rely on the podocytes for VEGF to maintain EC function, fenestrations between the ECs and adequate functioning of the glomerulus [10].

Once the VEGF signaling pathway is disrupted, podocytes become injured. One mechanism is thought to be brought by ET-1, ET-1, the most potent vasoconstrictor [21], is also released from ECs adjacent to podocytes within the glomerulus. This is mediated by raised sFLT-1 concentrations, reducing the protective paracrine VEGF signaling within the glomerular ECs.

ET-1 can directly act on podocytes, causing disruption of the cytoskeletal protein Nephrin within the slit diaphragms. The slit diaphragms regulate the permeability of the glomerular membrane, and therefore damage to this leads to proteinuria. Nephrin is linked to two main structural proteins; Synaptopodin and α-Actinin 4 [10]. The cellular injury that occurs from the response to the mediators in pre-eclampsia, such as ET-1, causes reduced expression of these structural proteins, leading to nephrin shedding [22], podocyte instability, and decreased selectivity of the slit diaphragms and podocyte loss [10], [23]. Consequently, nephrinuria and podocyturia develop prior to proteinuria [23]. Additionally, there is disruption of the autocrine co-receptor Neuropilin-1, contributing to decreased podocyte survival [10].

Translational research, to date, has shed minimum light on pre-eclampsia and associated complications. Primarily this is due to pre-eclampsia not being known to occur naturally in animals. However, pregnant rodents -although far from ideal to represent human pregnancy- display similarities to the relevant pregnancy-induced cardiovascular adaptations seen in pregnant women. Such adaptations include an increase in glomerular filtration rate (GFR) and renal plasma flow [24], a reduction in systemic vascular resistance (SVR) secondary to vasodilation [25], and an increase in cardiac output [26].

Through pharmacotherapy and genetic modifications, pre-eclampsia models could be replicated in mice facilitating research models. For example, in an animal-based trial [27], pre-eclamptic-like features induced in a mouse model were treated with an angiotensin receptor antagonist, losartan. However, this finding is of limited clinical value as losartan is teratogenic to human fetuses [28].

VI. REPRODUCTIVE MANIFESTATIONS IN PRE-ECLAMPSIA

Clinical manifestations of renal pathology in pre-eclampsia include proteinuria, proteinuria with nephrotic syndrome and AKI.

A. Nephrotic Syndrome

Nephrotic range proteinuria is the loss of 3 or more grams per day of protein in the urine. It complicates 0.32% of pregnancies, with preeclampsia contributing up to 0.19% (i.e. >50% of cases) [29], making it the leading cause of nephrotic syndrome in pregnancy [7]. A thorough review of the patient's history followed by investigations for pre-eclampsia and other biological markers will exclude differential diagnoses such as lupus nephritis, which may present de novo in pregnancy. Women with nephrotic syndrome usually need close follow-up, especially when remote from term, as delivery is the treatment for pre-eclampsia but not for other causes such as glomerulonephritis [30]. Occasionally a renal biopsy may be necessary for this distinction.

Women with nephrotic syndrome alone without significant hypertension or renal insufficiency usually have good outcomes.

Nephrotic syndrome is a hypercoagulable state. Complications such as deep vein thrombosis (DVT), arterial thrombosis, and rarer but similar thromboembolic events such as renal vein thrombosis and pulmonary embolism are known to occur in these patients. Even in values below nephrotic ranges, proteinuria in pregnancy is notoriously known to be a risk factor for thrombosis. Therefore, it is recommended to commence thromboprophylaxis with low molecular weight heparin in the presence of additional risk factors [31]. Those with severe proteinuria (uPCR>300 mg/mmol or ACR >250 mg/mmol) should be started on thromboprophylaxis with low molecular weight heparin antenatally and continued postpartum unless there is a specific contraindication [31].

Nephrotic range proteinuria developing before 20 weeks of gestation is unlikely to be due to pre-eclampsia, but rare cases of pure pre-eclampsia with nephrotic syndrome before 20 weeks have been reported in the literature [32].

B. Acute Kidney Injury in Preeclampsia

Renal insufficiency in pre-eclampsia is defined as a serum creatinine level >/= 1.1 mg/dl or a value doubling in the absence of renal disease [2]. Hypertensive disorders, especially pre-eclampsia and HELLP syndrome, are considered the most common causes of pregnancy-related AKI [33].

A retrospective cohort study from Canada on obstetric acute renal failure between 2003 and 2010 reported a significant increase in women with hypertensive pregnancy disorders, particularly pre-eclampsia. Apart from the
pathological processes in the kidney due to pre-eclampsia, the authors suggested that the rise could be consequential on some management aspects of preeclampsia, specifically fluids, antihypertensives and drug use that may have led to hypovolemia, renal hypoperfusion and nephrotoxicity [34].

The incidence of acute renal failure in pre-eclampsia and eclampsia is reported at nearly 5%, which is usually complicated by abruptio placentae, disseminated intravascular coagulation (DIC) and HELLP syndrome [35].

VII. MANAGEMENT OF PRE-ECLAMPSIA ASSOCIATED RENAL DYSFUNCTION

The definitive treatment of pre-eclampsia is delivery to prevent disease progression [30]. The timing of delivery is based on severity, maternal and fetal conditions and gestational age. Expectant management up to 37 weeks is recommended in women with gestational hypertension or pre-eclampsia without severe features. The mother and fetus need to be frequently evaluated for signs of disease progression during this period.

Changes in GFR and deranged renal function tests are signs of severe disease progression. Hyperuricaemia, more than 90th centile of typical pregnancy values, is the earliest change in renal function, followed by proteinuria [36]. The onset of heavy proteinuria (defined as >3g/24 hours) is not an indication of immediate delivery in all pregnancies. In such cases, careful monitoring of the fetus and mother is vital as deterioration can occur rapidly [36], [37].

Deteriorating renal function diagnosed by serum creatinine levels of more than 1 mg/dl, blood urea nitrogen of 13 mg/dl, or development of oliguria (urine output less than 500 mL/day) are indications for immediate delivery to prevent further damage to the kidneys. Renal function in pregnancy is assessed using serum creatinine concentrations as estimated GFR (eGFR) is not valid for use in pregnancy [31].

VIII. FACTORS AFFECTING RENAL FUNCTION IN THE PERIDELIVERY AND PERIOPERATIVE PERIODS

A. Control of Blood Pressure

Based on several reputable research studies [38]-[40], the European Society of Cardiology (ESC) and the USA National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEP) recommended the threshold for initiation of antihypertensive medications should be ≥150/95 mmHg for patients with pre-existing hypertension (HTN) and >140/90 mmHg for patients with gestational HTN (with or without proteinuria) and patients with subclinical hypertension-mediated organ damage [41], [42]. A target BP of <140/90 mmHg is favoured for all hypertensive pregnant women. The second trimester is usually associated with a physiological drop in BP; hence, some women become able to come off their antihypertensive medication [43].

In our institution, the antihypertensives labetalol, methyldopa, beta-blockers (other than atenolol) and slow-release nifedipine are considered first-line pharmacotherapies. If the pregnant woman’s blood pressure is well controlled on a medication pre-pregnancy, she may continue it during pregnancy, except for angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (which are teratogenic). Intravenous hydralazine, labetalol, and oral nifedipine are used for emergency BP control.

B. Magnesium Sulphate

Magnesium Sulphate (MgSO4) is the recommended drug of choice for preventing and controlling eclampsia (44). The mechanism of its anticonvulsant activity has not been clearly defined [44]. The primary effect is, however, thought to be central and hypotheses on this include elevating the seizure threshold by its action at the N-methyl D-aspartate (NMDA) receptor. Another proposed mechanism of action includes membrane stabilization in the central nervous system secondary through its actions as a nonspecific calcium channel blocker, in addition to decreasing acetylcholine transmission in motor nerve terminals [45]. Another theoretical mechanism of action is the promotion of vasodilatation of constricted cerebral vessels. This occurs by opposing the action of magnesium sulphate to calcium-dependent arterial vasospasm, reducing cerebral barotrauma [45].

MgSO4 is excreted by the kidneys. Women with renal insufficiency should, however, receive a standard loading dose of 4 grams since their volume of distribution is not affected, but a reduced maintenance dose should be tailored to the serum creatinine levels [44].

Clinical assessment for magnesium toxicity should be carried out at close intervals, namely every one-to-two hour, and the maintenance dose should be administered only when there are no signs of toxicity. MgSO4 clinical effects and toxicity is closely linked to its plasma concentration. A concentration range equal to or above 1.8 to 3.0 mmol/L has been suggested to treat eclamptic convulsions [45]. Maternal toxicity is rare when MgSO4 is careful administration and monitoring are followed. The earliest warning sign of impending toxicity in the parturient is loss of the patellar reflex at plasma concentrations between 3.5 and 5 mmol/L. Respiratory paralysis occurs at 5 to 6.5 mmol/L. Cardiac conduction is altered at greater than 7.5 mmol/L, and cardiac arrest can be expected when magnesium concentrations exceed 12.5 mmol/L. Careful attention to the monitoring guidelines can prevent toxicity. Deep tendon reflexes, respiratory rate, urine output and serum concentrations are the most commonly followed variables [45]. In women with compromised renal function, serum magnesium levels should be checked every four to six hours as an adjunct to clinical assessment.

C. Fluid Management

Maintaining an input-output chart is vital to avoid fluid overload as these patients are more prone to pulmonary oedema [46]. Maintenance fluid if the form of a balanced salt or isotonic saline solution at a rate of 80 mL/hour is recommended for a nil-by-mouth patient, provided that there is no ongoing abnormal fluid loss, such as bleeding [46]. Oliguria should be challenged with a modest fluid bolus (e.g., 300 mL), and where there is no response, this suggests renal insufficiency and should be managed cautiously to reduce the potential for iatrogenic pulmonary oedema [46]. In patients with renal insufficiency, it is crucial to readjust the
maintenance fluid delivery rate, taking into account the volume of fluid used to infuse other intravenous medications.

IX. RENAL REPLACEMENT THERAPY/DIALYSIS

indications for renal replacement therapy in pregnancy are similar to those in non-pregnant patients and include volume overload, hyperkalaemia refractive to medical management, metabolic acidosis and symptomatic uraemia [47]. Haemodialysis is generally used in acute life-threatening scenarios. Recommendations in pregnancy include increased dialysis time and frequency, keeping serum urea <45-60 mg/dL, and minimizing fluid shifts and hypotension not to affect fetal well-being [48]. In pregnancy-related AKI, renal replacement therapy is often short-term until there is recovery of acceptable renal function [47].

Hyperkalaemia is often managed conventionally by administering insulin, glucose, and ion exchange resin [3]. There are no published data about resin use in pregnancy, but this drug has a local action within the gastrointestinal tract; hence there are no anticipated fetal deleterious effects [3]. A 4 mEq/L decrease in bicarbonate concentration is common in a healthy pregnant woman. This must be considered when attempting to correct metabolic acidosis with sodium bicarbonate. Anemia associated with AKI should be corrected with blood transfusion in acute therapy where indicated [47].

X. FACTORS AFFECTING RENAL FUNCTION DURING DELIVERY

A. Monitoring

This should include standard and invasive monitoring as necessary. Invasive blood pressure measurements should be considered if time permits to provide continuous blood pressure monitoring and rapid response to adverse changes, especially during rapid sequence intubation, or if other complications, such as excessive bleeding, are expected. It will also facilitate frequent blood sampling to assess acid-base status. A central venous pressure (CVP) line can be used if intravenous access is challenging to administer vasoactive drugs or measure cardiac functions/preload. Trends in CVP readings might correlate with changes in preload values. Transthoracic echo can be used for cardiac monitoring, to assess volume status and guide fluid therapy.

B. Choice of Anesthesia

Renal dysfunction is not a contraindication for neuraxial anesthesia, which is preferred for pre-eclamptic patients because of a higher chance of difficult airway even where the patient is hemodynamically stable, and coagulation parameters and platelets are normal. Up to date evidence suggests that the risk of spinal epidural hematoma with a platelet count ≥70,000 × 10^9/L is likely to be very low in the obstetric patient, no matter what the underlying diagnoses is including gestational thrombocytopenia, immune thrombocytopenic purpura (ITP), and hypertensive disorders of pregnancy and it is reasonable to proceed with a neuraxial procedure if clinically indicated [49]. If there is a history of bleeding associated with thrombocytopenia or DIC, it would be wise to avoid neuraxial procedures and seek expert hematologic evaluation before proceeding with the neuraxial procedure [49]. If the platelet count is between 50,000 and 70,000 × 10^9/L, then weighing risks vs benefits justify proceeding with a neuraxial procedure [41]. The most crucial advantage of neuraxial anesthesia is that it avoids severe hypertension, which may occur during induction and emergence from general anesthesia and may be life-threatening. Neuraxial anesthesia may cause more hypotension than general anesthesia, but it is usually transient and easily treated, without a difference in neonatal outcome. It is believed that patients with pre-eclampsia may be at a lower risk of spinal-induced hypotension than those without.

In a recent study on the effects of dexmedetomidine on kidney injury of parturient with pre-eclampsia undergoing cesarean section under combined spinal-epidural anesthesia, dexmedetomidine infusion for 10 minutes before surgery was shown to exert protective effects on kidney injury [50].

General anesthesia may be indicated for emergency cesarean delivery where the patient has reassuring airway parameters or for those with severe coagulopathy such that neuraxial anaesthesia is contraindicated [51].

In addition to the commonly used anesthetic induction agents, other medications may be needed during induction to blunt the hemodynamic response to intubation, with a target blood pressure of systolic <160 mmHg and diastolic <110 mmHg [51]. Usually, drugs with rapid onset and short duration of action are preferred.

C. Perioperative use of Magnesium Sulphate

MgSO_4_ infusion should be continued intraoperatively during cesarean delivery. It causes muscle relaxation, potentiates the effect of non-depolarizing neuromuscular blocking agents (NMBAs), and thus can prolong their duration of action [52]. NMBAs of medium duration action are better avoided in women on magnesium undergoing cesarean delivery. Magnesium does not have a synergistic effect with succinylcholine, nor does it potentiate its action. The usual rapid sequence induction dose (i.e., succinylcholine 1 to 1.5 mg/kg i.v.) should be administered [52]. If it is necessary to augment the muscle blockade intraoperatively, small doses of NMB (e.g., rocuronium 10 mg i.v. or cisatracurium 2 mg i.v.) should be administered titrated to effect using a twitch monitor with the goal of one twitch in the train of four twitches [52].

D. Blood Pressure Measurement

Maintaining adequate renal perfusion to limit ongoing damage and reverse any pre-ischaemic changes is one of the essential principles in managing renal dysfunction due to pre-eclampsia. Therefore, the patient's blood pressure should be maintained close to her baseline, rather than normal blood pressures, to preserve uteroplacental perfusion, but always less than a systolic 160 mmHg and diastolic 110 mmHg. Vasopressors (e.g., phenylephrine and/or ephedrine) are routinely administered during the initiation of spinal anesthesia to prevent spinal hypotension. These vasopressors should initially be administered in small incremental doses, titrated to restore blood pressure close to the baseline reading. The choice of vasopressor should be based on maternal haemodynamics since selecting specific vasopressors has not
been shown to affect maternal or fetal outcomes in patients with preeclampsia [53], [54].

E. Fluid Management

The current obstetric practice limits total fluid administration in patients with severe pre-eclampsia-including oxytocin and magnesium infusions- to match the urine output and insensitive losses [55]. Intravenous fluid co-loading during placement of neuraxial anesthesia should be avoided or minimized in patients with severe pre-eclampsia to prevent circulatory overload. Replacement should be with fluids, blood, and blood products and strict input and output monitoring.

XI. FACTORS AFFECTING RENAL FUNCTION POST-DELIVERY OR SURGERY

A. High Dependency Unit (HDU)

Patients with renal dysfunction due to pre-eclampsia should be monitored postoperatively in a high dependency unit. Blood pressure control, correcting fluid and electrolyte imbalance, and maintaining adequate nutrition are supportive. Persistent acidemia, hyperkalaemia, volume overload and uraemia are indications for renal replacement therapy [56].

B. Postoperative and Postpartum Pain Management

Multimodal analgesia strategies for pain control should promote rapid recovery and ambulation and minimise the need for postoperative opioids [57]. Epidural analgesia can be continued for postoperative pain management to avoid or reduce the dose of drugs with renal elimination, such as morphine [58]. Pain control strategies include neuraxial morphine or hydromorphone, transverse abdominis plane (TAP) blocks, quadratus lumborum blocks, acetaminophen, and systemic opioids. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided for postoperative pain management because of the increased risk of renal injury [57].

XII. PROGNOSIS

Pre-eclampsia is associated with an increased risk of developing chronic kidney disease (CKD), particularly within five years of the affected pregnancy [59]. Endothelial function measured using flow-mediated dilatation (decreased in preeclampsia) improves weeks postpartum but may not normalize until four years after follow-up [60]. In one recent observational study, 15.3% of women with pre-eclampsia developed an AKI during pregnancy, and two-thirds had fully recovered renal parameters by the time of hospital discharge [61]. Pre-eclampsia, particularly early-onset pre-eclampsia, was strongly associated with several chronic renal disorders later in life. Furthermore, women with pre-eclampsia may be at increased risk of developing end-stage renal disease later in life, but the absolute risk is small [62].

Some studies showed that even dialysis-requiring AKI has a favorable prognosis with complete recovery of renal function in most cases. Thus, the majority (93%–100%) of patients with HELLP syndrome-related AKI have a near-complete reversal of renal dysfunction. Furthermore, progression to CKD is reported to occur in less than 10% of patients who developed AKI on pre-existing renal disease and/or hypertension [62].

XIII. POSTNATAL KIDNEY FUNCTION ASSESSMENT

Women with pre-eclampsia should be seen in the postnatal clinic 6–8 weeks after delivery. A urinary reagent-strip test should be carried out at this visit. Those with proteinuria (1+ or more) 6–8 weeks after the birth should be offered a further review with their general practitioner or a nephrologist three months after delivery to re-assess kidney function. Those with abnormal kidney function results should be referred to a nephrologist for further kidney assessment tests at three months.

XIV. RENAL BIOPSY IN PREGNANCY

Glomerulonephritis may develop or flare up in pregnancy and may be difficult to distinguish from pre-eclampsia clinically. Indication for a renal biopsy in pregnancy includes unexplained rapidly progressive renal failure and symptomatic nephrotic syndrome (29). The use of renal biopsy in pregnancy remains controversial and performing one may be considered reasonable if it results in a potential change in therapeutic management (63). The risk of various complications with a renal biopsy is higher during pregnancy compared to the postpartum period (7% versus 1%) (29).

XV. CHRONIC KIDNEY DISEASE AND PREECLAMPSIA

The diagnosis of superimposed pre-eclampsia in women with CKD is complicated by coexisting chronic hypertension and proteinuria [64], [65]; hence standard diagnostic criteria cannot be applied. In the absence of clear guidance or criteria to diagnose superimposed pre-eclampsia, a recent meta-analysis estimates a 10-fold increase in the overall risk for the development of superimposed pre-eclampsia in women with CKD compared with women without CKD [63], and preeclampsia affected 20% to 87% of pregnancies in women with CKD depending on pre-pregnancy disease stage and the diagnostic criteria used [64].

The prognosis of CKD and the morbidity associated with preeclampsia require distinction from the gestational change in CKD. Unless systemic or fetal complications of pre-eclampsia arise, it will remain challenging to distinguish superimposed pre-eclampsia from CKD. Although used, the diagnostic value of relative changes in blood pressure and proteinuria in pre-eclampsia remains unclear [64]-[68]. Angiogenic placenta growth factor (PIGF) and anti-angiogenic sFLT-1 biomarkers have been used to diagnose pre-eclampsia in the general population [69]-[71], with emerging data on their use as a diagnostic adjunct in pregnant women with CKD [65], [72], [73]. Once approved, this might bring hope to diagnosing this complicated scenario.
PARD may cause devastating materno-fetal outcomes and remains a vital obstetrics complication. The aetiology of PARD and findings are varied. Accordingly, this might help in improving diagnostic accuracy and introducing timely management. PARD occurs during pregnancy's late trimester and continues into the postpartum period. A small percentage will develop CKD later. Finally, prevention is the most effective method of dealing with this life-threatening condition. This is done by providing and promoting maternal education, high-quality and accessible antenatal care with equipped obstetrics facilities, early detection and diagnosis of the condition, and timely management.

**CONFLICT OF INTEREST**
Authors declare that they do not have any conflict of interest.

**REFERENCES**


