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Menstrual disorders in chronic kidney disease: causes and management

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Abstract

Chronic kidney disease is increasing in prevalence throughout the world. This leads to many hormonal changes in the body which in turn lead to variations in the menstrual bleeding patterns in premenopausal women. Dysfunction of the coagulation pathway is also seen with women developing either thrombotic tendency or bleeding disorder. This review paper examines the causative mechanisms of the endocrinological and bleeding disorders in kidney diseases. Decrease in kidney function affects the metabolism and excretion of medication used for treating these problems. The treatment modalities available for treatment of heavy menstrual bleeding in women suffering from chronic kidney ailments have been discussed to enable the treating physician to choose from options available to decrease the morbidity due to heavy menstrual bleeding and improve the quality of life.

Keywords: Chronic kidney disease, heavy menstrual bleeding, endocrinological changes, coagulation disorder

1. Introduction

1.1 Chronic kidney disease (CKD) is a huge global health burden affecting both the sexes equally. The global estimated CKD prevalence has been estimated to be between 11 to 13% and even as high as 17% with majority in stage 3^[1, 2]. The estimated percentage of the population diagnosed as CKD increases from 13.7% in the fourth decade of life to 34.3% in the eighth decade^[1].

1.2 Subsequent to kidney failure, there are various endocrine and hematological changes which can manifest as menstrual irregularities ranging from heavy menstrual bleeding (HMB) to amenorrhea. This review presents the pathophysiological changes that cause dysfunctional uterine bleeding in patients with CKD and the various modalities available for the treatment.

2. Causes and classification of chronic kidney disease

2.1 Chronic kidney disease is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health^[3]. CKD is classified based on cause, glomerular filtration rate (GFR) and albuminuria category.

2.2 The significant causes of CKD are hypertension, diabetes mellitus, atherosclerosis, renal artery stenosis, polycystic kidneys, lupus and other connective tissue disorders, drugs like analgesics and proton pump inhibitors, infections causing glomerular nephritis, gout, amyloidosis, hypercalcemia and malnutrition in childhood. Environmental and genetic factors and nephrotoxins (known and unknown) may also contribute significantly.

2.3 The staging of chronic kidney failure by GFR, as classified by the National Kidney Foundation-Kidney Disease Improving Global Outcome (KDIGO), 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease is reproduced in Table 1^[3].

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Table 1: Staging of Chronic Kidney Failure by GFR

GFR category	GFR (ml/min/1.73m ²)	Terms
G1	>90	Normal or high
G2	60-89	Mildly decreased, relative to young adult level
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney Failure

GFR: Glomerular filtration rate

3. Complications of chronic kidney disease

3.1 There are no serious clinical symptoms of chronic kidney disease till about 70-75% of functioning renal tissue is lost. As kidney function deteriorates, there are many complications including disorders in water-electrolyte balance, hyperkalemia, metabolic acidosis, pulmonary congestion, anemia, symptoms of uremia (lack of appetite, nausea, vomiting, pruritus, pericarditis, peripheral neuropathy, sleep disturbances, depression, coma), bleeding tendencies and various endocrinological imbalances (elevated growth hormone, prolactin and parathyroid hormone levels, thyroid hormone imbalance, changes in sex hormones levels and the hypothalamic-pituitary-adrenal functions and hyperinsulinemia and insulin resistance [4].

3.2 Gynecological problems are highly prevalent in women with CKD. Up to two-thirds have a menstrual disorder [5]. Secondary amenorrhea is seen in 50-100% of patients with end stage renal disease, many of whom start to menstruate when put on dialysis [6]. Of the patients who menstruate, 50-80% have polymenorrhea, oligomenorrhea or heavy menstrual bleeding (HMB) [6]. Premature menopause is also common. Disruption of either the hormone balance or coagulation issues due to defective platelet aggregation or alteration in coagulation factors can lead to HMB.

4. Hormonal changes affecting menstruation in patients with CKD

4.1 In CKD, the basal secretion of Gonadotropin releasing hormone (GnRH) is preserved, but the pulsatile secretion is lost, maybe due to Thyrotropin releasing hormone (TRH) induced hyperprolactinemia and high levels of GnRH and Luteinizing hormone (LH) due to decreased renal clearance [7, 8]. This causes loss of appropriate release of LH in mid cycle leading to anovulation but the exact stage of CKD when this suppresses ovulation is currently unknown [7, 9]. Increased circulating levels of endorphin due to reduced opioid clearance may also inhibit ovulation. Patients may have HMB or may develop amenorrhea. The median age of menopause in women with CKD is decreased to 48 years, from median of 52.5 years among healthy women [10, 11].

4.2 Endometrial changes seen in women with CKD have ranged from atrophy to proliferative changes in anovulatory cycles, glandular hyperplasia and rarely adenocarcinoma. Serum

progesterone levels are decreased, except in women with regular menses [12].

4.3 The hypothalamic dysfunction associated with CKD appears to be at least partially reversed with intensive dialysis and kidney transplantation [8]. Estradiol levels rise in response to clomiphene citrate administration, showing that ovaries remain responsive to GnRH pulses [8]. The endometrium also remains responsive to estrogen and progesterone. This is important for young women who want to try for pregnancy after a renal transplant.

4.4 CKD affects the peripheral metabolism and excretion of thyroid hormone. Elevated/ normal thyroid stimulating hormone (TSH), reduced free T4 and low T3 levels are noticed [13]. The prevalence of thyroid disorders ranges from 39-53% of patients, risk increasing with the stage of CKD [14, 15]. Menstrual problems are attributed to TRH induced increased prolactin levels, altered TSH and LH response, peripheral conversion of androgens to estrogens, decreased sex hormone binding globulin production and decrease in coagulation factors VII, VIII, IX, XI [16]. Dialysis does not significantly normalize the high TSH and low T3 values, but levels normalize after renal transplant [13].

4.5 Up to 30% of patients with CKD have elevated prolactin levels [17]. Both the decline of renal prolactin clearance and increased lactotroph resistance to dopamine contribute [9, 18]. Bromocriptine or cabergoline administration may be effective in treatment of patients presenting with amenorrhea or galactorrhoea [19]. 80% of patients on hemodialysis have hyperprolactinemia as the levels do not decrease with dialysis [20]. But renal transplantation results in normoprolactinemia, sometimes within a few days [17].

4.6 Hyperinsulinemia and insulin resistance occur in many patients when the GFR is <50ml/min/1.73m², due to decreased sensitivity to insulin, inadequate insulin secretion and increased hepatic gluconeogenesis [21, 22]. Hyperinsulinemia has been associated with menstrual irregularities due to ovulation dysfunction [23].

4.7 The hormonal changes leading to menstrual irregularities are summarized in table 2:

Table 2: Changes in the hormonal levels leading to menstrual irregularities in chronic kidney disease

Hormone	Secretion levels
GnRH	Basal- normal, pulsatile-absent
FSH	Premenopausal –levels as in follicular stage. Levels do not increase near ovulation. Menopausal - increased
LH	Increased, surge is absent
Serum estrogen	As in follicular stage. Do not increase and peak mid cycle
Serum progesterone	As in follicular stage. Do not increase in second half of cycle
TSH	Normal or increased
Free T3, Free T4	Decreased
Prolactin	Increased
Insulin	Increased, insulin resistance present

5. Coagulation disorders in CKD

5.1 During normal menstruation, there is vascular disruption after fall in progesterone levels, leading to onset of bleeding. Platelets aggregate, the coagulation cascade is activated and clot is formed. The fibrinolytic system is also activated to prevent clot formation in the uterine cavity.

5.2 Patients with CKD are prone to coagulation disorders, which may lead to either thrombotic or bleeding issues. Endothelial dysfunction and coagulation factor abnormalities are seen. In the uterus, unopposed estrogen causes endothelial dysfunction, contributing to disturbed endometrial angiogenesis, fragile vessels and defective hemostasis [24]. There is also a higher proportion of prostaglandin E and prostacyclin, rather than prostaglandin F, inducing vasodilatation instead of vasoconstriction [24].

5.3 There is an increase in coagulation factors, like von Willebrand factor, factor VIII, factor VIIa and fibrinogen, suggesting prothrombosis and decreased fibrinolysis [25]. Women with antiphospholipid syndrome with renal complications have thrombotic microangiopathy and vascular dysfunction, needing anticoagulation medication [26].

5.4 In later stages of CKD, the patients also develop platelet dysfunction, leading to bleeding tendencies and prolonged bleeding time. Several factors are thought to contribute to impaired platelet adhesion and aggregation, such as impaired influx of calcium and synthesis of thromboxane A₂ and, altered release of adenosine di-phosphate (ADP) and serotonin from platelet α -granules and faulty arachidonic and prostaglandin metabolism [27]. Uremic toxins like guanidinosuccinic acid stimulate nitric oxide release, which increase prostacyclin formation, change vascular tone and contribute to hemostasis disturbance [27]. During menstruation, derangement of the formation of the intravascular platelet plugs in the exposed subendothelial tissue leads to increased menstrual loss [24].

5.5 Anemia may play a role in increased bleeding tendencies because it decreases the availability of platelets near the vessel wall. Hemoglobin is also a scavenger of nitric oxide [27]. Improvement in hemoglobin levels results in improvement in platelet function in this population and a decreased bleeding time.

6. Clinical presentation and investigations

6.1 Though more than half the women with CKD have menorrhagia, secondary amenorrhea or attain an early menopause with menopausal symptoms, most do not seek a gynecology consultation. Women are likely to seek treatment only if they have concerns about future fertility, have HMB or need contraceptive advice.

6.2 A complete history should be taken followed by a thorough physical and gynecological examination. The bleeding pattern and flow and its impact on quality of life should be documented. Symptoms suggestive of anemia or any endocrinological imbalance and the medications taken should be noted. Family history of coagulation disorders, deep vein thrombosis and hormone sensitive cancers must be asked for. Physical examination, including a pelvic inspection and a bimanual examination should be performed. A cervical cytology for cervical dysplasia is required.

6.3 Work up for abnormal uterine bleeding is done to find out the cause of the bleeding. Though the fertility is low in patients with CKD, pregnancy should be ruled out. Identification of likely cause following the FIGO classification system (pneumonic -PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not otherwise classified) is done [28]. The investigations should include a complete blood count with platelets, serum iron, total iron binding capacity, TSH and serum prolactin levels in addition to renal function tests. Coagulation factors levels are measured if indicated. Evaluation with an ultrasound examination, hysteroscopy and endometrial sampling or other investigations is performed as needed.

7. Management of heavy menstrual bleeding

7.1 Management of menstrual disturbances, especially HMB, in a patient with CKD is determined by the age of the patient, amount of bleeding, desire for fertility or surgery and anemia. For example, a young patient may be waiting for a renal transplant following which she may want a pregnancy. The hormonal effects at all stages of CKD are thought to be reversible and normalization of the levels of FSH, LH, prolactin and estrogen is seen following renal transplantation [7]. Hence, an initial conservative approach with medical management is tried.

7.2 The levonorgestrel-releasing intrauterine system (LNG-IUS) is a first line treatment option for the treatment of HMB in CKD as it decreases monthly blood loss and is easily reversible. The subdermal implant is also a good progestin-only method [7]. These methods are appropriate for women on dialysis and renal transplant recipients also [7, 29, 30]. The risk of infection does not appear to be increased in these patients [29]. The LNG-IUS is more effective than oral progestogens in treatment of HMB, with a greater reduction in HMB, improved quality of life and is acceptable long term but it is associated with more minor adverse effects [30, 31].

7.3 Oral progestogen like medroxyprogesterone acetate (MPA) 10mg per day for 7 days is effective for acute moderate bleeding. Short cyclic regimens of MPA at 5 to 20mg daily for 7-10 days in luteal phase or long cycles from day 5 to day 26 of the menstrual cycle have been used for women with chronic HMB. Women using this regimen must use some form of barrier contraception, since it does not prevent pregnancy [32].

7.4 All oestrogen-based methods confer an increased risk of hypertension, venous thromboembolism, stroke, arterial disease and cervical cancers. However, in acute heavy bleeding caused due to endometrial atrophy or due to uremia, high doses of intravenous oestrogen can be used to control the acute episode of bleeding. The dose used is 0.6mg/kg body weight daily intravenously over 30-40 minutes for 5 days. Estrogens decrease bleeding time by decreasing the nitic oxide concentrations, increasing production of thromboxane A₂ and adenosine diphosphate, which help in platelet plug formation [33]. Estrogens also help in regeneration of the endometrium. The time to onset of action is about 6hrs, maximum effect at 5-7 days with duration of action 14-21 days [33]. Estrogen has been administered transdermally in the form of estradiol, <50 μ g daily, for periods up to 24 months, in refractory bleeding from various organ systems, as there is a lower incidence of thromboembolism and

7.5 Tranexamic acid (TXA), an anti-fibrinolytic, is a synthetic lysine derivative. It acts by competitively inhibiting activation of plasminogen [36]. It decreases HMB by about 50%. It is also used in uremic bleeding and during surgery in CKD patients. Improvement in bleeding time is seen in 24-48 hours [37]. Neurotoxicity, including retinal toxicity and seizures has been documented in patients with CKD on treatment with TXA [38, 39]. TXA is contraindicated in women with seizure disorders or a history of thrombosis [40, 41]. TXA is excreted through the kidneys and over 95% is excreted unchanged. The dose suggested is 10mg/kg body weight with at the rate of 0.5-1.5mg/kg/hour [41].

7.6 Non – Steroidal Anti Inflammatory Drugs (NSAIDs) like mefenamic acid, ibuprofen and naproxyn are prostaglandin inhibitors. They increase uterine vasoconstriction and platelet aggregation and decrease the menstrual bleeding modestly but other medicines like TXA and LNG-IUD are more effective [42]. NSAIDs should not be used in patients with CKD as they may worsen the kidney disease.

7.7 Desmopressin is a synthetic analog of vasopressin and it promotes the release of von Willebrand factor from the endothelial storage sites, improving the bleeding time. It is used to treat patients with bleeding disorders, like von Willebrand's disease and for patients who are taking antiplatelet agents requiring emergent invasive surgeries [43]. It is also used in correction of uremic bleeding at a dose of 0.3µg/kg i.v.in 50ml saline in 15-30 minutes or as 3 µg/kg intranasally. The time to onset of activity is 30-60 minutes, with duration of 4-8 hours [43]. Reduced urine volume and hyponatremia may be seen. Evidence on the effect of desmopressin in reducing menstrual blood loss is very limited. One study showed a reduction in blood loss compared to use of TXA [44].

7.8 Endometrial ablation techniques can be tried in non-responders to medical management of HMB who are not interested in conservation of fertility. In a series of 11 patients with CKD, who underwent transcervical resection of endometrium (TCRE), menstrual pattern improved in all, with 9 women achieving amenorrhea and none needed hysterectomy [45]. Radiofrequency endometrial ablation has also been found useful in 58 women, who were studied, with 89.7% achieving amenorrhea [46].

7.9 For premenopausal patients on hemodialysis, the lowest possible dose of heparin should be used. A patient on peritoneal dialysis may have hemo-peritoneum during menstruation or even during ovulation. Patient is managed conservatively if the bleeding is mild, but if the bleeding is heavy, patients need treatment with suppression of ovulation [47].

7.10 Hysterectomy is the definitive treatment for HMB in patients who do not respond to all other methods of treatment. The patients should receive dialysis the day before surgery to correct any acid-base imbalance, electrolyte abnormalities, volume status and to minimize bleeding and anesthesia complications so that postoperative dialysis can be postponed to up to 48 hours [48]. In case dialysis is required within 24 hours of surgery, anticoagulants are not used. Blood pressure control and careful fluid management is essential during surgery. Anemia is managed with blood transfusions. Case reports of patients on dialysis who have undergone hysterectomy for various reasons is encouraging [48, 49, 50]. In the United States, a nationwide

inpatient sample studied 2330 Stage 5 CKD and 4.4 million non-Stage 5 CKD patients who went hysterectomy from 2000-2011 and found that the mortality rates and post-operative complication rates were higher at 1.4% vs 0.1% and 24.3% vs 11.1% respectively [51].

7.11 Anaemia is common in CKD patients and is present in nearly all dialysis patients [52]. The target hemoglobin level to maintain in CKD patients is ≤ 11.5 g/dL. This is achieved with both iron therapy and with erythropoiesis stimulating agents.

7.12 Correction of uremic bleeding is accomplished through treatment of renal anaemia with recombinant human erythropoietin or darbepoetin alpha, adequate dialysis, desmopressin, cryoprecipitate, tranexamic acid or conjugated estrogens. Cryoprecipitate is indicated when patient is hemodynamically stable but in need of urgent surgery or control of bleeding; also for patients who are hemodynamically unstable but cannot tolerate extra fluid [33].

7.13 Disturbances of the thyroid and parathyroid levels and hyperprolactinemia are treated with medication. Post renal transplant, the hypothalamo-pituitary axis dysfunction is rapidly corrected, with ovulatory cycles resuming in a large percentage of women [53]. Women with either amenorrhea or HMB may resume normal cycles. Pregnancy is best avoided till one year post transplant. Contraception advice must be given before discharge from the hospital post successful transplant surgery.

8. Conclusion

8.1 Chronic kidney disease is a growing health problem with an increasing prevalence worldwide. There are a growing percentage of women in the reproductive age group with chronic kidney disease and consequent menstrual disturbances. Heavy menstrual bleeding can be controlled in a large number of patients with medical management, with hormonal and non-hormonal drugs. The doses of the drugs may need to be modified to avoid side effects. Endometrial ablation and definitive surgery is needed in non-responders. Anemia and nutrition status needs careful observation. Post successful renal transplant, hypothalamo-pituitary-ovarian axis function is restored in most women and menstrual cycles are regularized with the quality of life dramatically improving. Hence, physicians should actively ask for menstrual disorders in women and manage them at all stages of chronic kidney disease.

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