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1

Renal physiology and fluid and electrolyte disorders in pregnancy

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A B S T R A C T

The majority of women are healthy entering pregnancy and do not require measurement of renal function or serum electrolytes. Clinicians must remain alert to the possibility of renal as well as fluid and electrolyte disorders in pregnancy, as the presenting complaints are often vague and mistaken for the normal physiology of pregnancy. In this chapter, our objectives are 1) to review the renal physiology from a practical/clinical standpoint; 2) to provide the clinical obstetrician a case-based approach to fluid and electrolyte disorders commonly encountered in pregnancy; 3) to consolidate knowledge on renal physiology and fluid and electrolyte disorders in pregnancy with MCQs that are directly aligned with content; and 4) to highlight key practice points and present a research agenda.

Introduction

The majority of women are healthy entering pregnancy and do not require measurement of renal function or serum electrolytes. Indeed, the “Choosing wisely Campaign” advocates against routine measurement of unnecessary laboratory tests (www.choosingwisely.org). Clinicians must remain alert to

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the possibility of renal disorders in pregnancy, as the presenting complaints are often vague and mistaken for the normal physiology of pregnancy. In the presence of fluid and electrolyte disorders, patients may report symptoms of fatigue, nausea, muscle weakness, polyuria, and polydipsia, whereas relatives may be more apt to note confusion and overall change in mood. Clinicians who follow-up during pregnancies are familiar with the detection of edema and hypertension and should also have a high index of suspicion when blood tests demonstrate a high creatinine or a low sodium concentration.

In this chapter, our objectives are 1) to review the renal physiology from a practical/clinical standpoint; 2) to provide the clinical obstetrician a case-based approach to fluid and electrolyte disorders commonly encountered in pregnancy; 3) to consolidate knowledge on renal physiology and fluid and electrolyte disorders in pregnancy with multiple choices questions (MCQs) that are directly aligned with content; and 4) to highlight key practice points and present a research agenda. We present the article as four structured sections, wherein we present case descriptions, followed by a brief review of the normal physiology in pregnancy, and where applicable, diagnostic approach, and baseline investigations and management considering maternal and fetal well-being.

In this review, we demonstrate abnormalities of renal physiology electrolyte disorders, focusing on sodium and potassium. The reader is referred to other reviews on calcium and magnesium disturbances in pregnancy.

Renal filtration in pregnancy

- Case 1

A 23 year-old nulliparous woman presents to her family physician because she is concerned about her kidneys and high blood pressure given that her father was recently diagnosed with chronic kidney disease. Physical examination shows a blood pressure of 128/84 mmHg without other particularities. A renal workup is completed, and her creatinine level is normal at 70 μmol/L. The doctor provides reassurance and counseling on nutrition and healthy lifestyle.

Three months later, she is referred to an obstetrician at 12 weeks of gestation. During the visit, she mentions that her sister had pre-eclampsia last summer resulting in a cesarian section at 34 weeks of pregnancy and voices her own concerns. On physical examination, her blood pressure is 110/70 mmHg. A baseline workup is done, and usual follow-up at the obstetrical clinic is then organized.

At 36 weeks of pregnancy, she presents to the hospital with spontaneous rupture of membranes and is experiencing uterine contractions. She is first evaluated by the obstetric clerk who measures her blood pressure as 142/96 mmHg. Her blood pressure measurement is repeated to confirm elevation, and a workup ordered for pre-eclampsia is reassuring. The patient is admitted to the obstetrical ward and delivers a healthy female infant 8 h later.

At the 6 week postpartum follow-up for gestational hypertension, she reports great fatigue. Her husband has returned to working night shifts, and she is experiencing difficulties with breastfeeding. She reports tearfulness and a reduction in appetite. The blood pressure is measured as 125/80 mmHg, and blood workup performed shows that her creatinine level has returned to her prepregnancy value (Fig. 1). The physician schedules a follow-up appointment in 4 weeks to reassess her mood.

- Brief review of normal glomerular filtration in pregnancy

Case 1 illustrates the expected renal physiological changes in pregnancy that lead to a lower serum creatinine level as shown in Fig. 1. Table 1 describes the evolution of creatinine laboratory values in pregnancy relevant to renal physiology from antepartum to 6 weeks postpartum. Water and sodium physiology is covered in Cases 2 and 3, whereas potassium physiology is covered in Case 4.

The nephron is the functional unit of the kidney and can be divided into 3 distinct parts: 1) the glomerulus, responsible for the initial filtration of the kidney, 2) tubules, from the proximal tubule to the more distal collecting tubules, responsible for the selective reabsorption and secretion of several molecules (electrolytes, proteins, and glucose), and 3) blood vessels, composed of the afferent arteriole (before the glomerulus) and the efferent arteriole (after the glomerulus). Different parts of the tubules

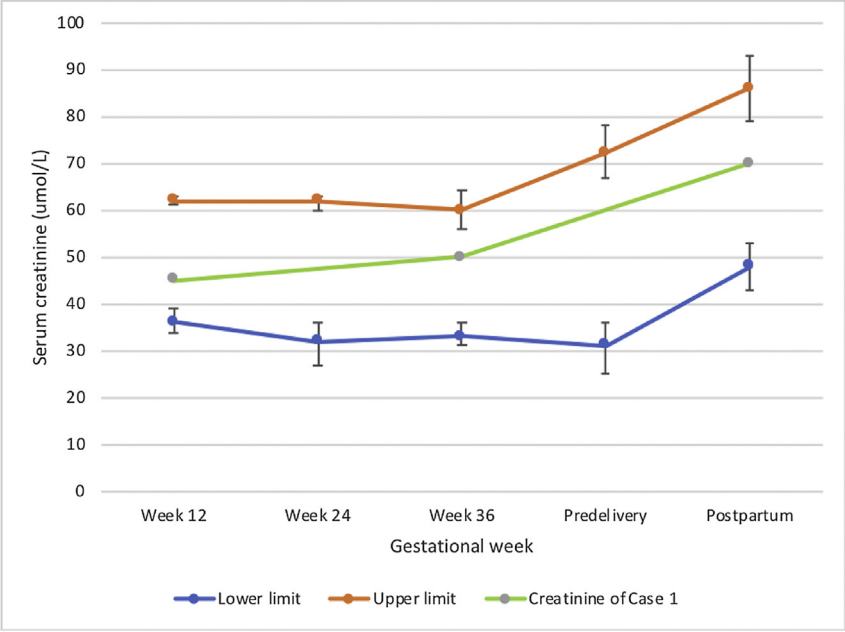

Fig. 1. Evolution of creatinine in normal pregnancy. The lower and upper limits represent the 2.5 and 97.5 percentiles for creatinine in pregnancy and postpartum.
Laboratory values are taken from Larsson et al. [4].

are responsible for the selective reabsorption of specific molecules such as glucose and amino acids for the active exchange of ions such as sodium and potassium through the sodium/potassium pump and for the secretion of others molecules such as urea and hydrogen ion to maintain homeostasis and lead to the final production of urine. Normal pregnancy alters filtration, reabsorption, and secretion in the nephron.

In the first half of pregnancy, an important increase in renal plasma flow and glomerular filtration rate takes place [1,3]. This gestational hyperfiltration occurs early in gestation and is directly linked to an increase in plasma volume (as described in section 2) and a decrease in vascular resistance, which accompany the increase in cardiac output. Vasodilatation of the afferent and efferent arterioles is caused by the active secretion of relaxin and nitric oxide and is largely responsible for the increase in renal plasma flow; this leads to the increase in the glomerular filtration rate by approximately 40% [1,3]. Glomerular hyperfiltration results in a large decrease in serum creatinine and urea in the first trimester that persists during pregnancy and returns to normal in the first weeks of the postpartum period [2].

Uric acid handling also undergoes important changes in pregnancy. Indeed, uric acid excretion increases secondary to a reduction in proximal reabsorption. Therefore, the serum uric acid level decreases by approximately 30% during the first two trimesters and returns to normal at the end of pregnancy [1].

Urinary protein excretion, including albumin and also larger proteins, is also altered in normal pregnancy [2]. Proteinuria as high as 300 mg per day is accepted in normal pregnancy. As further discussed in a review of renal physiology, this upper limit is somewhat arbitrary, as one of the largest studies performed in 270 pregnant women reported a mean 24 h protein excretion of 116.9 mg with an upper 95% confidence interval of 259.4 mg [3]. This increase in protein filtration is the result of the increase in glomerular filtration rate and an alteration of the proximal tubule's capacity for reabsorption of proteins [1]. Other plausible mechanisms have been proposed and are not be covered in the present chapter. The decreased reabsorption capacity of the proximal tubule also leads to glycosuria and calciuria in pregnancy [1–3]. This glycosuria should not be mistaken for diabetes mellitus [3].

Table 1
Pregnancy-specific ranges for laboratory values relevant to renal physiology.

Laboratory tests	Before pregnancy	12 weeks of pregnancy	24 weeks of pregnancy	36 weeks of pregnancy	6 weeks postpartum
Serum creatinine (μmol/L)	73 (11) [50–90]	52 (13) [25–79]	50 (12) [25–74]	58 (17) [23–93]	70 (10) [50–90]
Uric acid (mmol/L)	238 (50) [154–325]	163 (44) [75–251]	184 (33) [118–250]	252 (54) [144–360]	276 (52) [173–379]
Albumin (g/L)	41 (2) [36–46]	38 (2) [33–43]	33 (2) [29–37]	32 (2) [28–36]	42 (3) [37–47]
Sodium (mmol/L)	139 (2) [136–142]	135 (2) [131–139]	136 (1.6) [133–139]	136 (1.4) [133–139]	140 (1.2) [138–142]
Potassium (mmol/L)	4.3 (0.3) [3.7–4.8]	4.1 (0.35) [3.4–4.8]	4.1 (0.30) [3.5–4.7]	4.2 (0.24) [3.7–4.7]	4.2 (0.34) [3.5–4.9]
Magnesium (mmol/L)	0.79 (0.06) [0.69–0.92]	0.73 (0.06) [0.62–0.84]	0.73 (0.07) [0.59–0.87]	0.69 (0.05) [0.59–0.79]	0.74 (0.06) [0.63–0.85]
Bicarbonate (mmol/L)	26 (1.7) [22–29]	22 (2.0) [18–26]	22 (2.1) [18–26]	22 (2.0) [18–26]	26 (2.6) [20–31]

Mean (standard deviation); Reference range [2.5–97.5 percentiles].
Laboratory values are taken from Lockitch, [5].

Finally, the kidney compensates for respiratory alkalosis caused by the progesterone-induced stimulation of central respiratory centers by increasing the excretion of bicarbonate, thereby resulting in a compensatory metabolic acidosis (expected levels of 18–22 mmol/L). In summary, knowledge of the normal renal physiology is crucial for the correct interpretation of blood workup and to identify when "normal" laboratory results are actually abnormal [4,5].

Key points

- Pregnancy is associated with gestational glomerular hyperfiltration, which leads to an expected decrease in serum creatinine level.
- Uric acid handling is altered in pregnancy, thus leading to a decrease in uric acid levels, with a nadir reached at mid-pregnancy.
- Proteinuria as high as 300 mg per day is tolerated in pregnancy and should not worry the obstetrician in the absence of other findings suggestive of pre-eclampsia or other features of renal disease.
- The renal response to gestational respiratory alkalosis leads to lower bicarbonate levels in pregnancy.

Fluid overload/hyponatremia in pregnancy

- Case 2

A 20 year-old healthy primiparous women is hospitalized at 36 weeks of gestation for pre-eclampsia. She presents with high blood pressure, headache, and rapid weight gain. Her blood pressure is in the range of 150/100 mmHg; her reflexes are brisk, and her edema is generalized. The baseline blood workup showed that the hemoglobin level is 110 g/L, leucocytes 15×10^9/L, platelets 150×10^9/L, creatinine 65 μmol/L, uric acid 400 mmol/L, ALT 70 U/L, and total bilirubin 3 μmol/L. Proteinuria is 5 g/day, which is a high level. Fetal ultrasound is consistent with growth restriction below the fifth centile and decreased amniotic fluid but appears as normal flow on Doppler ultrasound. Initial management is instituted with antihypertensive drugs and magnesium sulfate, and the recommended plan for delivery at 37 weeks is discussed with the couple. The repeat blood workup for maternal surveillance reveals a sodium concentration of 126 mmol/L and albumin level of 25 g/L.

- Brief review of the normal physiology of sodium homeostasis in pregnancy

Early pregnancy is associated with systemic arterial vasodilation occurring secondary to hormonal changes along with an increase in cardiac output. Following the "underfill" paradigm, where the kidney and other baroreceptors sense a relative drop in the circulating volume, the renin-angiotensin system is activated, thereby promoting active sodium reabsorption into the proximal tubule [6,7]. Water passively follows sodium entry, thus resulting in an increase in the plasma volume observed in pregnancy. Concomitantly, the nonosmotic secretion of the antidiuretic hormone (ADH) by the posterior pituitary gland in pregnancy leads to a net gain of free water by increasing water retention in the collecting tubules independent of sodium reabsorption. Along with a lower osmotic threshold for thirst in pregnancy, the total body fluid balance is "more water than sodium," with the observation of plasma osmolality and plasma sodium, respectively, lower by 10 mosm/L and 4–5 mmol/L. Of note, ADH can also be released when acute volume depletion occurs as a mechanism to restore normal volume [8].

- Diagnostic approach and baseline investigation for hyponatremia

Hyponatremia is not simply a problem of insufficient sodium. When approaching hyponatremia, one can, as a first step, determine the plasma osmolality to exclude hyperosmotic and isosmotic causes as shown in Table 2 [9]. Cases of hyperosmotic hyponatremia secondary to uncontrolled diabetes with hyperglycemia will occasionally be encountered during pregnancy, whereas etiologies including hypertonic infusions such as mannitol are very rare. Similarly, isoosmotic hyponatremia (pseudo-hyponatremia) secondary to severe lipidemia or proteinuria is rarely seen in this population. Hence, the remainder of this section focuses on the approach to hypoosmotic hyponatremia.

Table 2 summarizes the most common causes of hypoosmotic hyponatremia, which is divided into three categories: hypervolemia, normovolemia, and hypovolemia [9]. Two concepts linked to normal physiology are crucial to understand hyponatremia in pregnancy: 1) hyponatremia as a result of excess water and 2) edema as a result of excess water and salt. Thus, cases of hypervolemic hyponatremia generally exhibit an active renin-angiotensin system with the combined antidiuretic effect of ADH. A point to emphasize is that determination of the cause of hypoosmotic hyponatremia is often based on a thorough history and detailed physical examination in addition to the baseline laboratory workup to confirm the clinical impression. Workup consists of plasma sodium and osmolality in addition to urine sodium, osmolality, and creatinine and aim to exclude potential causes—when indicated—with serum creatinine, urea, and uric acid; liver function tests with coagulation panel; albumin; complete blood count; thyroid-stimulating hormone (TSH); cortisol; urinalysis; and proteinuria. Additional investigations are instructed as appropriate (e.g., discovery of decompensated cirrhosis, nephrotic syndrome not related to pre-eclampsia, and fluid overload from peripartum cardiomyopathy). Of interest, hyponatremia can occur in both nephrotic (as per Case 2) and nonnephrotic cases of pre-eclampsia [10–12]. One also needs to consider a combination of factors that induce hyponatremia in pregnant women (e.g., liberal water intake or the administration of hypotonic fluids or medication in conditions that increase the release of ADH, such as pain or severe nausea [8,13,14].

- Management with maternal and fetal considerations

Hyponatremia is relatively frequent in the peripartum period, and most cases have a spontaneous resolution without any maternal or fetal complications resulting from a lower sodium level. In one study, hyponatremia $\leq$130 mmol/L occurred in 26% (16/61) of women receiving more than 2500 ml of oral and intravenous fluid during labor [15]. Treating the cause or removing an offending cause or drug when identified will often suffice (Table 2). The need for correction with hypertonic saline is presently rarely indicated and reserved for symptomatic cases (e.g., confusion, seizures) or severe acute hyponatremia (<120 mmol/L) [16,17]. The medication should be administered under very close monitoring and in consultation with expert advice to avoid rapid correction and prevent osmotic demyelination syndrome (previously central pontine myelinolysis) [9], a severe and often irreversible complication for which young women are particularly susceptible [18].

In the setting of inappropriate secretion of ADH (also often transitory), mild water restriction may suffice to partially correct hyponatremia. Only in selected cases not responding to water restriction,

Table 2
Clinical approach to hyponatremia in pregnancy.

STEP 1	Measure plasma osmolality
• If hyperosmotic (Posm >300 mmol/L) → Consider uncontrolled diabetes with hyperglycemia or hypertonic infusions (rare) • If isosmotic (Posm = 275–300 mmol/L) → Consider severe lipidemia or proteinuria (rare) • If hypoosmotic (Posm <275 mmol/L) → Proceed to STEP 2	
STEP 2	Evaluate volemic status
• If hypervolemia → Proceed to PART 1 • If normovolemia → Proceed to PART 2 • If hypovolemia → Proceed to PART 3	
PART 1 – Hypervolemic hypoosmolar hyponatremia causes	
• Normal pregnancy • Hypotonic solute • Nephrotic syndrome • Congestive heart failure • Cirrhosis	
Management strategies • Avoid hypotonic solute • Treat underlying cause • Water and salt restriction	
PART 2 – Normovolemic hypoosmolar hyponatremia causes	
• Drugs (e.g., oxytocin and DDAVP) • SIADH (e.g., pain, nausea and vomiting, drugs, central nervous system illness, or pulmonary infection) • Stress • Hypothyroidism • Adrenal insufficiency • Potomania	
Management strategies • Avoid/discontinue offending drugs • Treat underlying cause • Water restriction • Sodium tablet and/or furosemide in selected cases of SIADH not responding to water restriction • Hypertonic saline (only in selected cases under very close monitoring to avoid rapid correction, with an aim to increase plasma sodium <12 mmol/24 hours)	
PART 3 – Hypovolemic hypoosmolar hyponatremia causes	
• Gastrointestinal loss (e.g., vomiting such as in hyperemesis gravidarum and diarrhea) • Renal loss (e.g., Bartter syndrome, osmotic diuresis, and diuretics) • Third space (e.g., ovarian hyperstimulation syndrome and pancreatitis) • Skin loss (e.g., extensive skin burns)	
Management strategies • Water and salt replacement (oral or intravenous fluid according to clinical status) • Treat underlying cause	

DDAVP: Desmopressine; Posm: Plasma osmolality; SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion.

sodium tablet and/or furosemide may be considered under close monitoring of fluid balance and serial laboratory testing. There is insufficient human data with regard to the use of vasopressin antagonists in pregnancy (tolvaptan and conivaptan) [19]. Available information is mostly limited to animal data (consultation with the Centre IMAGe, August 2018; www.chusj.org/fr/soins-services/P/Pharmacie/Centre-IMAGe).

It is interesting to know that the physiology of the fetal–maternal unit is such that the neonate can also present with neonatal hyponatremia that can be symptomatic. This finding emphasizes how water concentration is rapidly equilibrated across the placenta. In addition, fetal hyponatremia can be further accentuated by the secretion of fetal ADH at the time of delivery [20]. It is wise to alert the pediatricians to the possibility of symptomatic neonatal hyponatremia when in the presence of severe maternal hyponatremia at the time of delivery.

Key points

- When sodium is decreased beyond the expected 5 mmol/L drop in pregnancy, one should not hesitate to extend the workup for an underlying cause.
- Hypervolemic hypoosmotic hyponatremia can occur in both nephrotic and nonnephrotic pre-eclampsia.
- Management of hyponatremia is usually limited to the removal or treatment of the underlying cause; severe hyponatremia should be managed in consultation with expert advice.
- Neonatal hyponatremia needs to be anticipated, as it can be symptomatic and lead to neonatal complications.

Diabetes insipidus in pregnancy

- Case 3

An 18 year-old primiparous woman consults at 34 weeks of gestation because she has felt unwell for several days. She was seen 2 weeks ago for regular follow-up. At that time, she had reported new-onset generalized pruritus without a rash for which she was prescribed an emollient cream. She was also given a 2-week leave from work because of excessive fatigue and nonrestorative sleep. At that visit, the blood pressure was measured as 108/74 mmHg, and the fetal ultrasound showed a normal biophysical profile. Since the last visit, she has developed nausea and vomiting and complains of worsening thirst. Her fatigue is compounded by multiple awakenings secondary to polyuria. She consults today because she has a new abdominal discomfort and wonders whether she is in labor. On physical examination, the patient appears unwell with mild icterus. Vital signs include a blood pressure of 100/50 mmHg with a pulse of 112 beats per minute and a respiratory rate of 18 per minute. Her mucous membranes are dry, and there is no venous distension or peripheral edema. There are no other findings on cardiovascular or respiratory examination. Abdominal examination shows a palpable liver edge with some tenderness on palpation, negative Murphy's sign, and no tenderness in the loins. Reflexes are brisk and symmetric with 1 beat of clonus bilaterally. Fetal monitoring does not reveal regular contractions.

Blood workup shows a hemoglobin level of 125 g/L, a hematocrit of 0.38, leucocytes of 15.8×10^9/L, and platelets of 160×10^9/L. Other results include sodium 140 mmol/L, potassium 4.7 mmol/L, chloride 106 mmol/L, creatinine 158 μmol/L, urea 12 mmol/L, albumin 28 μmol/L, ALT 700 U/L, uric acid 250 mmol/L, total bilirubin 54 μmol/L, amylase 110 U/L, and lipase 250 U/L. The protein/creatinine ratio is estimated as 0.02 mg/mmol. The nurse soon reports a urine output of 1.2 L for the previous 4 hours.

- Brief review of water homeostasis in pregnancy

Gestational diabetes insipidus occurs particularly during the third trimester and is a condition that illustrates the unique physiology of pregnancy [21,22]. Diabetes insipidus is a condition of excessive polyuria and polydipsia resulting outside pregnancy from the inadequate output of ADH and/or a failure of the kidney to respond to ADH. Polyuria and polydipsia can also occur during pregnancy and

postpartum associated with other mechanisms, thereby leading to diabetes insipidus, which we review further.

In pregnancy, the trophoblasts (mass increased by 1000) produce a large amount of vasopressinase, a cystine aminopeptidase that inactivates ADH, also known as vasopressin, by the cleavage of the N-terminal aminated portion [7,23]. The vasopressinase activity shows a 40- to 50-fold increase during pregnancy. There is also a marked capacity (a fourfold increase) of the liver to degrade the circulating vasopressinase. For the regulation of water retention, the ADH released by the posterior pituitary gland is also increased during pregnancy along with more renal aquaporin 2 receptors expressed in the collecting tubules [7,23]. Conditions that interfere in the maintenance of equilibrium between the production and/or degradation of ADH and vasopressinase result in inappropriately higher water excretion.

For instance, conditions associated with decreased ADH production include central lesions such as prolactinoma or craniopharyngioma. Degradation problems can occur in settings such as increased placental mass (e.g., twin pregnancy with more production of vasopressinase), leading to enhanced degradation of ADH. Alternatively, hepatic dysfunction associated with decreased vasopressinase clearance leads to excessive renal water excretion, thereby resulting in increased diuresis (i.e., polyuria, defined below) [24–26].

- Diagnostic approach and baseline investigation for diabetes insipidus

Diabetes insipidus is probably underdiagnosed during pregnancy because women frequently report an increase in urinary frequency and feel thirsty. Hence, the recognition of a syndrome of polyuria and polydipsia is often minimized. The frequency of diabetes insipidus is estimated to 2–6 cases/100,000 pregnancies [27], and several causes have been identified in pregnancy (Table 3). In some cases, a combination of contributing factors is required for diabetes insipidus to become clinically apparent. In addition, pregnancy may unmask a prior subclinical condition (e.g., twin pregnancy in a woman with previous transsphenoidal surgery). Polyuria is usually defined as urine output >3–3.5 L/day, but lower urine volume would also be abnormal during dehydration and/or hypernatremia.

First, different causes of polyuria need to be considered when a pregnant woman complains of polyuria and polydipsia (Table 4). The history is of utmost importance to determine notable changes not only in urine frequency but also in urine volume (including nocturia with large volumes of urine voided), marked increase in thirst and water intake during both day and night. Drinking habits and beliefs regarding water intake before pregnancy should also be evaluated. Finally, medication use as well as past medical history (e.g., craniopharyngioma) should be noted. A calendar of intake and diuresis is useful as is a 24 h urine collection to confirm the presence of polyuria. Signs of dehydration and weight loss need to be evaluated along with potential fetal secondary effects (e.g., oligohydramnios), particularly in acute presentations. Initial workup for polyuria consists of plasma and urine osmolality, plasma sodium, glucose, and calcium. The workup for causes of diabetes insipidus related to pregnancy includes pre-eclampsia, hemolysis with elevated liver enzymes and low platelet count (HELLP) syndrome, and acute fatty liver of pregnancy (the latter illustrated in Case 3). Maternal and fetal well-being should also be assessed. When appropriate, further evaluations include a magnetic resonance imaging and pituitary function tests to determine central causes of diabetes insipidus. Where available, plasma ADH and vasopressinase can be instructed in the diagnostic workup of diabetes insipidus. Recently, copeptin has been proposed to replace the water dehydration test to distinguish causes of polyuria, but data are scarce as to its diagnostic value particularly in pregnancy [28–30]. If absolutely required, the water dehydration test should be performed under very close monitoring of vital signs and diuresis [21]. Serial laboratory tests should be done at least every 30 minutes with immediate return of results (stat orders) to closely document changes in sodium levels and prevent complications from rapid shifts in natremia and iatrogenic acute dehydration.

- Management with maternal and fetal considerations

Most cases of gestational diabetes insipidus are transitory, and when not severe, oral compensation for water loss is sufficient to prevent dehydration and hypernatremia. In these cases, no further

Table 3
Clinical approach to diabetes insipidus in pregnancy.

If diabetes insipidus is diagnosed, consider either ①,②, or ③
① **Antepartum causes (pre-existing condition)**: an imbalance between increased vasopressinase and inadequate ADH production and/or reduced renal sensitivity to ADH
• Central diabetes insipidus (e.g., prolactinoma, craniopharyngioma, histiocytose X, and transphenoidal surgery or trauma) • Nephrogenic diabetes insipidus (e.g., obstructive nephropathy, congenital diabetes insipidus, and lithium – less likely in young women without prolonged drug exposure)
② **Peripartum causes (pregnancy-related causes)**: a balance between increased vasopressinase-degrading ADH, decreased circulating vasopressinase, and/or decreased hepatic clearance
• Increased placental mass (e.g., multiple pregnancy) • Acute fatty liver of pregnancy • Pre-eclampsia/HELLP • Liver disease/dysfunction • Idiopathic
③ **Postpartum causes**: decreased or abolished central release of ADH
• Sheehan syndrome • Autoimmune hypophysitis • Hypopituitarism • Other

ADH: Antidiuretic hormone; DI: Diabetes insipidus; HELLP: Hemolysis-Elevated Liver Enzymes Low Platelet count.

Table 4
Causes of polyuria in pregnancy.

• Hyperglycemia • Hypercalcemia • Diabetes insipidus • Potomania • Saline overload • Other causes of osmotic diuresis unlikely in pregnancy (e.g., mannitol, urea, and bicarbonate)

treatment is needed in addition to addressing the underlying cause. Prompt hypotonic intravenous fluid replacement is required if the patient is nauseated and vomiting, if the patient's oral intake is limited (as in prolonged labor or when fasting for a procedure including cesarian section), or when any cause of volume loss is not well counterbalanced by oral intake (e.g., profuse diarrhea and hemorrhage). Careful monitoring of blood pressure, heart rate as well as input and output balance, weight, and plasma sodium is required to prevent complications from severe dehydration and hypernatremia, along with fetal monitoring. In selected cases and under close monitoring, desmopressin (or DDAVP) can be administered to reduce water loss. DDAVP (1-deamino-8-D-arginine vasopressin) is a synthetic analog of vasopressin deaminated in the N-terminal portion and thus not degraded by vasopressinases [7]. It can be administered under various forms (intravenous, oral, and intranasal) and is compatible with both pregnancy and breastfeeding [31,32]. Caution needs to be exercised in transitory gestational diabetes insipidus to not over-correct the polyuria and hypernatremia and induce iatrogenic hyponatremia, which could lead to further maternal complications such as seizures.

Key points

- Consider gestational diabetes insipidus and its causes (or combination of factors) in the presence of polyuria and polydipsia and/or high normal sodium level or overt hypernatremia in pregnancy.
- Document 24 h urinary volume along with intake as well as initial blood and urine workup for diabetes insipidus.
- Anticipate risk of increased sodium when access to free water is restricted and plan accordingly to prevent complications. Clear communication with both patients and health professionals along with close monitoring is paramount, especially during the peripartum period.

- DDAVP is compatible with pregnancy and breastfeeding and should be limited to selected cases.

Hypokalemia in pregnancy

- Case 4

A 27 year-old primiparous woman presents to the obstetrical clinic at 12 weeks gestation complaining of weakness and fatigue. She is not known to have any past medical history. She denies any urinary or gastrointestinal symptoms other than morning sickness without significant emesis. She takes three meals per day with healthy snacks between meals. Her vitals are stable with a blood pressure of 90/65 mmHg and a pulse of 90 beats per minute. She is eupneic at rest. Her heart, lungs, and abdomen examinations are all normal, and she denies any muscle pain.

Preliminary blood workup shows sodium 136 mmol/L, potassium 2.4 mmol/L, creatinine 60 μmol/L, normal complete blood count, and TSH. The patient is referred for a consultation in obstetrical medicine where an extended blood workup including electrolytes and a venous blood gas was instructed. The latter shows metabolic alkalosis and a low magnesium level of 0.42 mmol/L; calcium and phosphate levels are both normal. Potassium (120 mmol per day divided as 3 doses of oral potassium chloride) and magnesium (1500 mg per day divided as 3 doses of oral magnesium gluconate) supplements are initiated with electrolyte follow-up once a week. At 28 weeks of pregnancy, intravenous potassium is administered to the patient because the potassium level remains at 2.9 mmol/L despite given a large dose of oral supplement. At delivery, precautions are taken to ensure that her potassium level is above 3.5 mmol/L and her magnesium level above 0.60 mmol/L. She delivers a healthy baby at 37 weeks of pregnancy. An evaluation in pediatrics is asked to assess the baby for any electrolyte abnormalities. An electrolyte follow-up is done at 6 weeks postpartum and shows a serum potassium level of 3.1 mmol/L and magnesium level of 0.65 mmol/L.

Case 4 illustrates a pregnant woman with Gitelman syndrome, an autosomal recessive genetic disorder characterized by hypokalemia that responds poorly to potassium supplements and features hypomagnesemia and metabolic alkalosis [34–38]. The presence of a tubular defect has a significant impact on the maintenance of potassium and magnesium homeostasis in pregnancy and can lead to maternal complications (arrhythmia, muscle spasm, and paralysis) [36]. Although the fetus seems to be protected from the maternal hypokalemia [34], it can be severely affected by the concomitant hypomagnesemia with a risk of fetal growth restriction and miscarriage [36].

- Brief review of the normal physiology of potassium in pregnancy

Serum potassium levels are principally controlled by a balance between reabsorption (cellular and proximal tubular uptake) and secretion (collecting tubule) [33]. In pregnancy, the renal secretion of potassium is increased by the elevated glomerular filtration rate and the activation of the renin-angiotensin-aldosterone system [36–38]. In return, an increase in progesterone levels and a systemic vasodilation counterbalance these effects to maintain a normal or slightly lower potassium level [34–36,38]. In counterpart, the elevated glomerular filtration rate in pregnancy promotes a net loss of magnesium in urine, resulting in mild hypomagnesemia [37].

- Diagnostic approach and baseline investigation for hypokalemia

A systematic approach of hypokalemia as shown in Table 5 helps the clinician with diagnosis and institution of the correct treatment. First, the clinician needs to rule out causes of cellular redistribution, such as insulin, beta-2-agonists, and increased catecholamine production. These categories of hypokalemia quickly improve with the removal of the causal agent or with a small dose of potassium supplement. A complete history excludes gastrointestinal loss of potassium caused by hyperemesis gravidarum, chronic malnutrition, repeated diarrhea, or laxative abuse. These are frequently accompanied by other electrolyte abnormalities such as hypomagnesemia and hypophosphatemia.

Table 5
Clinical approach to hypokalemia in pregnancy.

STEP 1	Exclude cellular redistribution
• Exclude diabetes with insulin therapy • Exclude increase in catecholamine release/stress • Exclude asthma with B-2-agonist therapy • Hypokalemic periodic paralysis	
STEP 2	Exclude gastrointestinal loss or poor intake
• Exclude hyperemesis gravidarum • Exclude important diarrhea or laxatives abuse • Assess intake to exclude poor oral intake	
STEP 3	Renal loss → Measure blood pressure
• If high blood pressure → Consider hyperaldosteronism (primary or secondary) → Consult obstetrical medicine or other relevant specialist • If normal or low blood pressure → Proceed to step 4	
STEP 4	Renal loss → Assess acid-base status
• Metabolic alkalosis ◦ Tubular defect → Gitelman syndrome, Bartter syndrome ◦ Diuretics → Loop diuretics, thiazides ◦ Important emesis • Metabolic acidosis ◦ Tubular acidosis or diabetic ketoacidosis	
Management strategies	Treat underlying cause Electrolyte supplementation
• Potassium supplement ◦ Oral → Potassium chloride, potassium phosphate, potassium citrate ◦ Intravenous → Potassium chloride, potassium phosphate (maximum 10–20 mmol per hour by a peripheral vein and up to 40 mmol per hour by a central line under monitoring in an intensive care unit[a]) • Magnesium supplement ◦ Oral → Magnesium gluconate, magnesium oxide, magnesium glucoheptonate ◦ Intravenous → Magnesium sulfate (maximum 2 g per hour under monitoring in an intensive care unit[a])	

[a] To adapt according to hospital protocol.

In the absence of either a cellular redistribution or gastrointestinal loss, further workup is needed to rule out renal loss of potassium by checking serum creatinine, complete serum electrolytes (sodium, potassium, magnesium, and chloride), urinary potassium, venous blood gas, and an electrocardiogram [37]. A complete physical examination is also necessary. Consultation with a medical specialist such as obstetrical medicine can be helpful at that time [37]. A high blood pressure guides the clinician toward a diagnosis of hyperaldosteronism caused by a secreting adrenal nodule or by a renal artery stenosis as seen in fibromuscular dysplasia. A normal or low blood pressure may lead the clinician toward a completely different differential diagnosis in which the evaluation of acid–base status is helpful. Indeed, the presence of metabolic alkalosis raises the suspicion of tubular defect caused by a genetic syndrome (Gitelman or Bartter syndrome) or the use of diuretics (loop and thiazides), although less likely in pregnancy. These clinical entities can be associated with other electrolyte abnormalities like hypomagnesemia for Giltelman and hypercalciuria for Bartter syndrome.

- Management with maternal and fetal considerations

The management of hypokalemia entirely depends on the etiology (Table 5). As mentioned, a hypokalemic cellular redistribution will respond well to the withdrawal of the causative agent and/or a small amount of potassium supplement. Gastrointestinal loss of potassium also responds to the treatment of the underlying cause and oral or intravenous potassium supplementation. If

gastrointestinal loss is chronic, whole-body potassium reserves can be largely depleted. Such a large depletion needs larger total amount of potassium supplement that can take a long time to correct. In case of renal loss of potassium, nutritional advice and potassium supplementation are the cornerstones of the treatment [35]. Large doses of oral or intravenous potassium are needed, with regular measurement of the serum potassium level [35–37]. The safe use of potassium-sparing diuretics such as spironolactone, eplerenone, and amiloride in pregnancy remains a concern. While some reassuring data exist for treatment with amiloride and spironolactone in pregnancy, much less data are available for eplerenone [32]. The concern of feminization of the male fetus is also present with the administration of aldosterone antagonists [34–37]. Further studies and more experience are needed to permit the use of these agents with confidence. The presence of hypomagnesemia should be appropriately treated with oral or intravenous magnesium and regular follow-up of the magnesium level [34,36].

A delivery plan must be developed with the relevant specialist and obstetrician in conjunction with neonatology/pediatrics to establish the desired potassium and magnesium target level before delivery as exemplified in Case 4. Moreover, a follow-up in pediatrics or neonatology should be requested soon after delivery to investigate and manage any electrolyte abnormalities in the newborn.

Key points

- Because potassium levels are not often routinely measured, clinicians should remain alert to the possibility of hypokalemia in the presence of unusual fatigue or muscle weakness.
- Hypokalemia in pregnancy can have different causes that should be thoroughly investigated.
- Hypokalemia secondary to renal loss requires a specific workup that includes physical examination, creatinine, complete electrolytes, and venous blood gas.
- While nutritional advice and potassium supplementation are the cornerstone of the treatment of hypokalemia caused by renal tubular defects, the safety of potassium-sparing diuretics is still being determined.

Summary

Basic knowledge of renal physiology in pregnancy allows the obstetrician to adequately interpret blood workup throughout pregnancy. It is important to remember the expected changes in serum creatinine and electrolytes along with the acid–base status to recognize when results that were labeled as normal are actually abnormal. It is also important to consider electrolyte disorders in the presence of vague symptoms that are beyond the usual complaints of pregnancy. For instance, nausea, fatigue, and muscle weakness as signs of electrolyte imbalance can be missed just as significant polyuria and polydipsia may be rapidly dismissed. In addition, clinicians should be on the lookout for electrolytic changes when using certain medications (oxytocin and DDAVP) and in the presence of certain diagnoses (e.g., acute fatty liver of pregnancy, pre-eclampsia, and nephrotic syndrome).

Practice points

- Abnormal renal function needs to be recognized when serum creatinine is not decreased as expected or when a rapid increase occurs, even if the value remains within usual laboratory intervals.
- Low sodium may be seen in a variety of clinical settings such as pre-eclampsia and as a result of medication use (e.g., oxytocin and DDAVP).
- Diabetes insipidus, both in its gestational forms or as a result of acute fatty liver of pregnancy, may be missed by clinicians because of adequate water intake and then decompensate in settings where intake is limited.
- In the presence of hypokalemia, the use of a simple step-based approach for the initial investigation allows the rapid institution of the appropriate management in pregnancy.
- Reference ranges from laboratories are for the nonpregnant population, and therefore, pregnancy-specific ranges need to be applied to pregnant woman.

Research agenda

- Development of better methods to determine renal filtration in pregnancy.
- Clarification of the roles of vasopressin antagonists in pregnancy (indication and safety data).
- Determination of the roles of copeptin in the diagnosis of diabetes insipidus in pregnancy.
- Collection of more safety data on potassium-sparing agents for hypokalemia in pregnancy.

Conflicts of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2018.11.008.

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