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Renal disease and pregnancy - Multiple choice answers vol. 57

1. a) F b) T c) T d) T e) F

Counselling should begin as early as possible in the care of women with kidney disease, to enable future planning and time for women to receive and process information. The nature of counselling will vary depending on the CKD stage. Avoiding an unplanned pregnancy is important for maternal and fetal health. Planning for pregnancy may take time and it is important to have contraception in place during this time. Qualitative studies in which women with kidney disease have been interviewed about their perspectives suggest that fear from medical catastrophizing causes distress and disengagement from the clinical interaction. Identify the needs and values of women, developing trusted clinical relationships, involving a multidisciplinary team and care partners, and delivering information in a sensitive manner takes a substantial investment of time. Each woman may each require different approaches to counselling, based on their experiences, values and needs. These should be elicited at the beginning of pre-pregnancy counselling.

2. a) F b) T c) F d) F e) T

Shared decision-making is a well-established concept and is known to contribute to better patient outcomes and experiences, including in maternity care. While there is little data in women with kidney disease directly and further research in this area is required, principles of shared decision-making can be utilised for this cohort. Deliberate and explicit consideration of patient perspectives and opinions, in conjunction with provision of best available evidence to underpin health care choices, can aid shared decision making and holistic, personalized care. While clinical assessment of risk is important and should be communicated sensitively to women, shared decision-making about pathways to pregnancy and pregnancy care is still necessary. A multidisciplinary team is recommended, and may meet to discuss the case. However informed, shared decision-making with the patient is still recommended, and this may convey the thoughts of the multidisciplinary team which can assist decision-making. Women with kidney disease and other chronic medical disorders in pregnancy report that fragmented care reduces communication of information and can cause confusion, therefore integrated models of care with a clear clinical lead is preferable.

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3. a) F b) T c) T d) F e) T

Serum levels of LH levels are higher in women on dialysis but normal variation within the menstrual cycle is lost. The absence of a midcycle surge in LH concentration means that ovulation is not triggered. Oestrogen levels are lower in women on dialysis. In the normal menstrual cycle, high level of oestrogen sensitise the pituitary gland to the effects of gonadotrophin-releasing hormone contributing to the surge in LH and subsequent ovulation. Low oestrogen levels in women on dialysis confer negative feedback to the hypothalamic-pituitary axis, meaning ovulation fails to occur. Renal clearance of prolactin is reduced in women on dialysis. This mimics the physiology of lactation with inhibition gonadotrophin releasing hormone release from the hypothalamus and anovulation. Women on dialysis have oligo/anuria due to impaired clearance by the kidney, not due to anti-diuretic hormone secretion. Cyclophosphamide is used in the treatment of rapidly progressive glomerular disease and is known to be gonadotoxic, leading to dose- and age-dependent ovarian failure.

4. a) F b) F c) T d) T e) F

Male and female condoms have typical-use failure rates of 18% and 21% respectively. This means that approximately 1 in 5 couples will conceive an unintended pregnancy during the first year with typical use. Condoms can however be used to prevent sexually transmitted infection. Combined oral contraceptives contain a combination of oestrogen and progesterone. Oestrogen confers an increased risk of arterial thrombosis including stroke, myocardial infarction and peripheral vascular disease. Dialysis is associated with a significantly increased risk of vascular disease and the additional use of oestrogen containing contraceptives is likely to increase a woman's overall risk to an unacceptable level. The progesterone implant (Nexplanon®) is a progesterone-releasing device, which is inserted under the skin and has a perfect- and typical-use failure rate of 0.05%. It is effective for 3 years and does not have the risk associated with oestrogen use. The intra-uterine system (Mirena®) is a progesterone-releasing intra-uterine device, which has a perfect- and typical-use failure rate of 0.2%. It is effective for 5 years and does not have the risk associated with oestrogen use. Intensive dialysis has been associated with an increased pregnancy rate compared to standard dialysis. Safe and effective contraception should be offered to women who wish to avoid pregnancy, especially if they are receiving an increased number of hours of dialysis.

5. a) F b) F c) F d) F e) F

An elevated blood pressure prior to dialysis may reflect the accumulation of fluid between dialysis sessions, chronic hypertension, or pre-eclampsia. A urine PCR >30mg/mmol in women with CKD, including those on dialysis, may be caused by underlying renal disease or pre-eclampsia. In women on dialysis, who have little or no residual renal function, clearance of serum creatinine is only achieved with dialysis. A rise in serum creatinine would be therefore expected in between dialysis sessions. Increased surveillance for fetal growth restriction is important for women on dialysis. An estimated fetal weight <10th centile is small for gestational age. The diagnosis of fetal growth restriction due to pre-eclampsia requires an assessment of growth velocity over time. There is emerging evidence from small cohorts and case reports that concentrations of sFlt-1 and PlGF have a comparable profile in CKD and superimposed pre-eclampsia to that shown in pre-eclampsia in the absence of CKD. However, the effect of impaired renal clearance and the sensitivity and specificity of a sFLT-1/PlGF ratio for the diagnosis of pre-eclampsia in women on dialysis is unknown.

6. a) T b) T c) F d) F e) T

Numerous cohort studies demonstrate a trend of improved pregnancy outcomes with longer dialysis time in pregnancy. Meta-analysis of contemporary data shows that dialysis frequency and dialysis duration have an inverse correlation with rates of preterm delivery and small for gestational age infants. Multivariable modelling of data from a large dialysis cohort showed that midweek blood urea nitrogen was significantly associated with gestation adjusted fetal weight, and that urea >12.5mmol/L had a sensitivity of 88% and an odds ratio of 6.4 (CI: 1.4–30.0) for adverse fetal outcome. Evidence that dialysis should be intensified for women newly commenced on haemodialysis in pregnancy in the same way as for women established on dialysis prior to pregnancy does not exist. In a study of intensive dialysis in pregnancy, a subgroup analysis of 17 women commencing haemodialysis after conception found no difference in gestational age at delivery between those receiving 33 ± 6 hours/week compared to 15±4h/week. Meta-analysis data demonstrating improved outcomes with intensification of dialysis do not include women starting dialysis after 20 weeks so should not be generalised. Residual renal function may underlie these findings. Elective Caesarean delivery is not required for the coordination of dialysis and circuit anticoagulation at the time of delivery. Indications for Caesarean delivery in women on dialysis are the same as for those in the general obstetric population. Pregnancy outcomes following successful kidney transplantation are significantly better than pregnancy outcomes on dialysis. Consensus advice is to wait until graft function is stable, at least one year after renal transplantation, on immunosuppressants known to be safe in pregnancy (calcineurin inhibitors, prednisolone).

7. a) T b) T c) F d) F e) T

During pregnancy plasma volume expansion alongside a rise in cardiac output increases renal plasma flow, leading to a rise in glomerular filtration rate. Hyperfiltration results in reduction in serum urea and creatinine concentration. Proteinuria increases during pregnancy, with values up to 300 mg/24 hours being normal and is attributed to the increase in glomerular filtration rate, alterations in the glomerular basement membrane and reduced proximal tubular reabsorption.

8. a) F b) F c) F d) F e) T

Pyelonephritis, placental abruption and hyperemesis gravidarum are most likely to cause AKI by a pre-renal mechanism, by hypotension in relation to sepsis, haemorrhage and hypovolaemia secondary to dehydration respectively. Renal stones can cause post-renal AKI by obstruction of the ureters. Thrombotic thrombocytopenic purpura is a thrombotic microangiopathy. Thrombotic microangiopathies are defined by the finding of fibrin and/or platelet thrombi in the microvasculature (arterioles and capillaries) of several organs, but primarily the kidneys and brain, and as such cause intrinsic renal damage. Histological features in the kidney include endothelial cell swelling, debris and protein in the subendothelial layer and splitting of the glomerular basement membrane.

9. a) T b) T c) F d) T e) T

This aspect of supportive management is central. Timely correction of renal perfusion by appropriate resuscitation with fluid and/or blood products is crucial to prevent the transition from a pre-renal insult to one causing intrinsic renal damage and potential long term damage. The causes determine the approach to replacement of blood and fluid losses. The clinician must distinguish between renal insufficiency caused by hypovolemia or hypotension and cases where acute tubular injury or cortical necrosis is present as the therapy for these conditions differs greatly. The administration of large

amounts of fluid where acute tubular injury or cortical necrosis is likely, is potentially harmful because of the risk of fluid overload with subsequent pulmonary congestion. The diet should avoid potassium and phosphate as well as provide high-quality, but not excessive protein. The clinician should remember that inadequate intake of calories also promotes catabolism. A systematic review and meta-analysis showed no benefit of low-dose dopamine infusion on renal function in acute renal failure or reduction in need for dialysis outside of pregnancy.

10. a) F b) F c) T d) F e) T

A decrease in serum creatinine is effectively seen in pregnancy but is associated with an increase in GFR that is secondary to the rise in renal plasma flow as a result of vasodilatation in the first trimester. This phenomenon is called gestational hyperfiltration and can lead to an increase in GFR around 50%. Glycosuria is very frequent in pregnancy and is therefore not necessarily linked to gestational diabetes. In effect, the majority of glycosuria in pregnancy is a result of a physiologic change in the proximal tubular reabsorption of glucose. A drop in uric acid is effectively seen in pregnancy and caused largely by an increase in kidney excretion. This increase is the result of a change in proximal uric acid reabsorption and an increase in tubular secretion. Indeed, we do tolerate as high as 300 mg per day of proteinuria in pregnancy, but it is mainly a result of a decrease in proximal tubule reabsorption of proteins leading to an increase in excretion. There is actually no evidence for loss of size selectivity by the glomerulus in pregnancy. Serum bicarbonate is decreased to 18–20 mmol/L as a result of an increase in urinary loss during pregnancy. This represents a normal renal compensation in response to the mild respiratory alkalosis triggered by the central stimulation of respiratory control by progesterone leading to hyperventilation.

11. a) F b) F c) F d) T e) F

There are few symptoms and signs of pre-eclampsia in this patient and therefore no clear indication for $MgSO_4$ therapy. Although a mildy symptomatic hyponatremia is present, this approach is too aggressive. Young women are at significant risk of complications from a too rapid or an overcorrection of the hyponatremia. Such complications include serious and potentially irreversible or even lethal neurological complications. Because the cause of the hyponatremia is most likely medication-induced, the first step would be to review the indication of the medication causing the hyponatremia and withdraw if possible. This patient does not meet the classical criteria for even mild post-partum hemorrhage. There are no indications to resume uterotonic or initiate anti-fibrinolytic therapy. However, this patient should be monitored closely for delayed postpartum hemorrhage as it is expected that the pregnancy-induced increase in VW protein and factor VIII levels will be followed by a rapid return to pre-pregnancy levels which can be associated with delayed-onset bleeding. In addition, it is important to know that oxytocin is structurally similar to vasopressin. Prolonged infusions of oxytocin may lead to water retention and hyponatremia. The hyponatremia is most likely secondary to DDAVP therapy. In addition to its hemostatic properties, Desmopressin is a synthetic vasopressin which exerts an antidiuretic effect by reducing water excretion at the level of the renal tubular cells. This leads to a decrease in serum osmolality and hyponatremia in the presence of concentrated urine. In the absence of a clear indication for a third dose of DDAVP, the medication should be stopped to allow for water excretion and correction of the electrolytic imbalance.

12. a) F b) T c) F d) F e) F

There are no symptoms or signs of congestive heart failure to substantiate a diagnosis of peripartum cardiomyopathy. An inappropriate secretion of ADH has been reported in states of pain and prolonged labor as well as in the presence of nausea. This is the likely diagnosis in this case in the absence of other

causes of SIADH (e.g. drugs, central nervous system illness or pulmonary infection) and with the exclusion of adrenal insufficiency and hypothyroidism. The increased urine osmolality argues against potomania but her habit of drinking large amounts of water may contribute to the severity of hyponatremia. Adrenal insufficiency can be excluded on the basis of an elevated cortisol, normal potassium, and in the absence of clear hypotension. There is no proteinuria on urinary dipstick. In nephrotic syndrome, we would expect a proteinuria > 3–5g/L associated with generalized oedema and serum albumin <30g/L. Severe cases may even be associated with albumin levels <20g/L and an increase in thrombotic risk.

13. a) F b) F c) T d) F e) F

Corticosteroids, azathioprine and calcineurin inhibitors (ciclosporin and tacrolimus) have been used extensively during pregnancy with an acceptable safety profile. Mycophenolate mofetil and mycophenolic acid are teratogenic, leading to 50% first trimester miscarriage and 23% serious congenital malformations in surviving infants. Ramipril and other angiotensin converting enzyme inhibitors (ACEi) are teratogenic in the second and third trimesters leading to renal agenesis and skeletal malformations. Very large cohort studies have not identified an increase in congenital abnormalities in pregnancies limited to first trimester exposure as compared with other hypertensive agents and after adjusting for confounding comorbidities. Discontinuation of ACEi is recommended prior to pregnancy in most women, however in women with proteinuric CKD, ACEi withdrawal risks increased proteinuria to nephrotic levels, symptomatic oedema, volume redistribution, pre-renal acute kidney injury and progressive CKD. Women should perform regular (at least monthly) pregnancy tests upon discontinuation of contraception and stop ACEi as soon as a successful pregnancy is suspected.

14. a) F b) T c) F d) F e) T

The incidence of delivery <34 weeks was 40% in women with CKD stage 3 in the largest published cohort study, and almost 80% were born prior to 37 weeks. The majority of cases of preterm delivery are iatrogenic due to clinician concerns about maternal or fetal health, rather than spontaneous preterm labour. It is unusual for patients with CKD stage 3 to progress to needing dialysis during pregnancy and pre-pregnancy dialysis preparation is not required. In women with eGFR<30, however, 1 in 3 will require renal replacement therapy within a year of pregnancy. Caesarean sections are performed more frequently in women with CKD than the general population – almost 80% in a recent study of women with CKD stage 3 – however this should be determined by obstetric issues rather than as a result of CKD *per se*. The incidence of pre-eclampsia or superimposed pre-eclampsia is reportedly about 40% in women with moderately severe CKD and 70% with more severe stages, although challenges remain in differentiating the clinical syndrome of pre-eclampsia for CKD progression or relapse of underlying renal disease.

15. a) F b) T c) T d) F e) T

SCr should return to pre-pregnancy values within the first 6 weeks post-partum in women with kidney disease and a normal to elevated (≥90 ml/min/1.73m2) or mild reduction (60–89 ml/min/1.73m^2) in eGFR prior to pregnancy. However women with moderate to severe renal impairment (CKD Stage 3–5, SCr ≥ 177 μmol/l, SCr 2.0mg/dL) are more likely to have an adverse renal prognosis in the post-partum period, with 1 in 5 women (with pre-pregnancy SCr values of ≥124 μmol/l (SCr ≥ 1.4mg/dL) sustaining a reduction in eGFR of up to 20% by 1 year post-partum. Mild hydronephrosis during pregnancy is a normal clinical finding in response to the effects of progesterone on uterine smooth muscle and ureteric compression from the gravid uterus. Renal pelvicalyceal dilatation can be present postpartum

and normally resolves within the first few weeks after the pueperium. Urinary protein excretion increases during pregnancy and becomes significant at levels of ≥300mg per 24 hours (≥30mg/mmol on 'spot' urine PCR testing). Physiological increases in proteinuria during pregnancy can take up to 3 months after delivery to normalise. Assessment of proteinuria is also contraindicated in women who are experiencing postpartum per vagina bleeding.

16. a) T b) T c) F d) T e) T

The gestational rise in glomerular filtration rate that is usually observed in pregnancy is diminished. This is accompanied by accelerated decline in renal function during and after pregnancy. Renal adaptation to pregnancy is reduced in women with more severe renal impairment but thresholds at which this fails to occur have not been clearly defined and is likely to vary between individuals. Impaired adaptation is due to pre-existing glomerular sclerosis and renal arteriosclerosis increasing systemic and renovascular resistance. This 'high-pressure' maternal circulation cannot adapt to hemodynamic changes of pregnancy inducing further renal parenchymal and vascular damage. One third of women with CKD who demonstrate stable eGFR from early in pregnancy will show deterioration between delivery and six months postpartum with just under one third of women demonstrating an initial decline after 6 months postpartum in all stages of CKD. Accelerated reduction in eGFR postpartum is associated with urinary protein of greater than 1g/24 hours.

17. a) T b) F c) T d) F e) T

NICE Guidance recommends the discontinuation of methyldopa in the postpartum period due to a side-effect profile including sedation, postural hypotension and low mood. Enalapril and captopril are excreted in only small amounts in breastmilk and are unlikely to be associated with harm. ARB safety in breastfeeding has not been investigated and therefore they are currently contraindicated. Tacrolimus and ciclosporin are safe to use postpartum and whilst breastfeeding and recommended treatment for lupus nephritis when accompanied by therapeutic drug monitoring. Mycofenolate mofetil (MMF) can be used in severe renal relapse in the postnatal period but due to the high profile of teratogenic side effects when used in the first trimester contraception counselling is imperative. Due to a lack of safety data, avoidance of MMF in breastfeeding is recommended.

18. a) T b) F c) T d) T e) T

HELLP syndrome occurs in 10–20% of cases of pre-eclampsia and is characterised by hemolysis, elevated liver enzymes and low platelet count. It is treated by delivery of the baby and placenta and therefore distinction from other TMAs of pregnancy is essential. Absence or deficiency in ADAMTS-13 (an enzyme that cleaves von-Willebrand factor) is associated with thrombocytopenic purpura and activity would be expected to be greater than 10% in women with aHUS. Assessment of ADAMTS-13 is paramount to diagnosis where the clinical picture remains indistinct for TMA-related disorder. Eculizumab is an alternative complement pathway inhibitor and has replaced plasma exchange as the gold standard treatment in aHUS. Since its introduction there has been a significant reduction in the incidence of end-stage renal disease and improved prognosis. Although not licensed for use in aHUS in pregnancy, there are some safety data in the treatment of paroxysmal nocturnal hemoglobinuria in pregnancy.

Eculizumab renders patients susceptible to meningococcal infections warranting vaccination prior to commencement of treatment and close monitoring for early signs of meningococcal infections.

19. a) F b) F c) T d) T e) F

"There is a higher chance of your baby being born below expected weight and prematurely, and this is likely to be related to how impaired your renal function is" as well as "We don't know if your kidney disease might have independent effects on your baby further on through their childhood" are the correct statements.

20. a) T b) T c) T d) F e) F

Combined maternity and renal care are a vital component to ensure optimal outcome. Involvement of a neonatologist is invariably helpful due to the high rate of preterm delivery. A paediatric nephrologist would rarely be required if there is a known fetal renal problem or an inherited one that was likely to affect a child. A psychologist should only be required in the event of adverse psychopathology.

21. a) F b) T c) F d) F e) F

Tools to estimate GFR are actually likely to overestimate the severity of renal disease and the main issue for their utility is pregnancy related physiological change.

22. a) F b) F c) F d) T e) F

One of the principles of prescribing drugs in pregnancy is to ensure that the expected benefit is greater than the risk to the fetus. Although there is a risk of infections causing harm to the fetus, the shortest duration and smallest effective dose of an antibacterial agent must be used. Care must be taken in the first trimester and agents selected which have established safety data. Clarithromycin is a macrolide antibiotic which has been studied in over 3000 pregnancies. The data does not show an increased incidence of malformations of any kind, but is not conclusive enough to rule out any fetal effects. Although it may be used where clinically indicated, an alternative such as erythromycin should be used if possible. Penicillins are generally safe to use in pregnancy. However, data on individual agents may vary. Co-amoxiclav carries a risk of necrotising enterocolitis if there are ruptured membranes and it is given close to delivery. However, amoxicillin and penicillin V (phenoxy-methylpenicillin) have no documented incidences of major malformations or adverse outcomes (with the exception of a possible link between amoxicillin and cleft palate which has yet to be confirmed). Tetracyclines have a documented risk in the second and third trimesters. Staining of children's milk teeth and disruption of enamel has been widely reported and there is also a risk of effects of bone growth, which has not been studied in the long term but has been documented in a few cases. Not all tetracyclines exhibit this effect, but further work is required to confirm these findings. 4-Aminoquinoline compounds are contra-indicated in pregnancy.

23. a) T b) T c) T d) T e) F

Timing of drug administration and breastfeeding is important to minimise the exposure of drug/metabolite to the newborn. Drugs with long half-lives should be avoided and information sought on timing of peak milk levels. Mothers can be advised to feed during low milk levels of the drug. The lower exposure of a drug to newborns will minimise the likelihood of adverse effects. However, this is not always a good indicator, as in the case of drugs with inherent toxicity (e.g. cytotoxics), decision thresholds will change. This is usually the case but not always. Some drugs may not be orally absorbed, but may alter oral and gut flora, causing adverse effects such as diarrhoea and thrush. Also, small amounts of a very toxic drug may have adverse effects on the newborn.

24. a) F b) T c) F d) T e) T

The standard equations used to estimate renal function cannot be used in pregnant mothers. eGFR is based on the MDRD equation and this has not been validated for use in pregnancy. Cockroft-Gault equation uses the patient's weight as a surrogate for estimated creatinine levels and does not take into account pregnancy. A reduction in serum albumin will lead to a higher free fraction of the drug, thus leading to more drug available for action on receptors. This is equivalent to increasing the dosage of certain drugs and can lead to unintended adverse events. Drugs which have a low level of protein binding will not increase their free fractions to a significant degree in hypoalbuminaemia. These agents already have the majority of their total serum level available as free drug, so any percentage increase from the loss of albumin will be clinically negligible in most circumstances. However, care will still need to be taken with drugs that have a narrow therapeutic window. Laying down of fat stores in pregnancy can indeed lead to reservoirs of fat soluble drugs and longer half-lives.