Renal Disease and Pregnancy

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1. Introduction

Pregnancy in women with different renal diseases has important consequences for the developing fetus and maternal health. Kidneys and the urinary tract have to adapt to the pregnancy status and therefore suffer significant anatomical, hemodynamic and endocrine changes. Failure to adapt can aggravate the preexisting maternal disease and can also create suboptimal environment for fetal development and increase the risk of obstetric complications. Knowledge and correct interpretation of the renal functional tests is necessary for the modern obstetrician, avoiding an incorrect diagnosis for renal disease where only specific renal changes during pregnancy are present, but meanwhile a correct evaluation of the renal function and changes can detect a pathology that can aggravate both the mother’s and the baby’s condition. Improvement and better understanding of the renal pathophysiology in pregnancy made possible that pregnant woman look forward for a good outcome, including here also the women with renal transplant. Nowadays is underlined the concept of multidisciplinary teamwork, a very important concept of modern medicine. The obstetrician should consider nephrologists as key players in the team and in our opinion should refer to them the pregnant women for a routine check-up of the renal status in the 2nd or beginning of 3rd trimester by ultrasound, beside the usual blood and urine analysis. The nephrologists and urologists should be involved in the management of severe medical conditions, such as preeclampsia, acute and chronic renal failure and never the less in the complex management of dialysis or renal transplant patients. In pregnancy it can be encountered several renal diseases, some of them preexisting the pregnancy and other developed or being direct influenced by pregnancy. This chapter will discuss briefly the basic evaluation of renal status in order to present and better understand the acute and chronic renal disorders in pregnancy. The chapter will focus on the most common preexisting diseases in pregnancy such as: chronic glomerulonephritis, secondary glomerular nephropathies, interstitial nephropathies (chronic pyelonephritis, renal tuberculosis), diabetes nephropathy, unique surgical kidney, chronic renal failure. From the renal diseases directly influenced by pregnancy it will be discussed: asymptomatic bacteriuria, symptomatic urinary infection, urolithiasis and acute renal failure in pregnancy.

It will be presented also the management of dialysis in pregnancy and pregnant women with renal transplant.
2. Evaluation of the renal function in pregnancy

Evaluation of the renal function is very important in pregnant women. *Serum uric acid, blood urea nitrogen (BUN), and serum creatinine levels* are important indices of renal function in pregnancy. Urinalysis is a useful tool for screening, further testing being necessary if changes in renal status are detected. Another useful method is the *24 hour urine sample*, used especially for total protein analysis. Most investigators consider the value of up to 260 mg/day of total urinary protein normal in pregnancy. Usually higher values indicate a decline of renal function due to preeclampsia. It should be noted that when serial 24-hour urine samples are performed in order to evaluate the change of renal status, it is crucial that the collection be standardized [Airoldi, 2007]. The total amount of creatinine excreted in 24 hour is considered to be the best method to compare two urine samples, as the cleared creatinine in a day should remain constant through pregnancy. The significance of dipstick or microscopic hematuria in pregnancy is uncertain, but some studies suggested it is associated with a greater risk for preeclampsia [Brown, 2005]. A study of McNair and collaborators compared urinalysis with uroculture for screening of asymptomatic bacteriuria [McNair, 2000]. They found that urinalysis has a sensitivity of 80.6% and specificity of 71.5% in their population. Given the 19.4% of false negative rate and the morbidity of the undiagnosed bacteriuria it is recommended that urine culture should be used as the primary method for screening in pregnant women. Although baseline creatinine clearance is decreased in patients with chronic renal insufficiency, it should still be elevated in pregnancy. Pregnancy may lead to permanent worsening of renal function in more than 40% women with serum creatinine (SCr) of 250 μmol/l or greater or creatinine clearance < 50 ml/minute and therefore it should serve as a contraindication to pregnancy. However, at that level of impaired renal function fertility is reduced and pregnancy is rare. The treatment of microalbuminuria with ACE-inhibitors should be interrupted in women that want to become pregnant. A moderate decrease of creatinine clearance is often observed during late gestation in women with renal disease. Typically this decrease is more severe in women with diffuse glomerular disease and it usually reverses after delivery. The long-term effect of pregnancy on renal disease remains controversial. Pregnant women with renal disease that have normal or near normal renal function at conception and a SCr < 120 μmol/L carry only a slightly increased risk of a long-term damage to their kidneys from pregnancy compared with never pregnant women with mild renal disease. In a larger multicenter study, 40% of women with moderate renal impairment (SCr 124-168 μmol/L; 1.49-1.90 mg/dL) had pregnancy related deterioration in renal function that persisted after delivery in almost 50% of cases [Williams, 2004]. One of the series from this study showed that only 2% of the pregnancies in women with initial SCr below 2.00 mg/dL rapidly decline to ESRF [Jungers, 1995; Jones, 1996; Epstein, 1996; Sibai, 2002]. Two-thirds of women with SCr > 2.0 mg/dL have a gestational deterioration in renal function that nearly always persists in the post-partum period. The recovery of the renal function after the delivery is rare. One third of women will develop ESRF during or following pregnancy. If renal function significantly worsens during pregnancy, studies showed that the termination of pregnancy will not improve the maternal outcome, therefore abortion cannot be routinely recommended for pregnant women with SCr over 1.5 mg/dL. Ideally before conception counseling should be provided for women with renal chronic disease. Severe hypertension is considered to be the greatest threat to pregnant woman with chronic renal disease, as uncontrolled hypertension can lead to intracerebral hemorrhage, or worse renal status. Diastolic blood pressure > 110
mmHg or greater will develop in ~ 20% of the patient with hypertension, a bigger chance of eclampsia being present in these cases. Proteinuria usually increases in chronic renal disease during pregnancy often reaching nephrotic ranges. A study remarked a correlation between low serum albumin and low birth weight [Studd, 1969].

Estimated glomerular filtration rate is another useful marker of renal function that depends on the value of serum creatinine and variables like patient age and gender. In the United Kingdom, estimated glomerular filtration rate is usually calculated using the four-variable Modification of Diet in Renal Disease (MDRD) formula although importantly this is not validated for use in pregnancy and it is inaccurate at values greater than 60 ml/min [Hall, 2010].

3. Pregnancy and underlying chronic renal disease

Historically, pregnancy has been commonly regarded as very high risk in women with chronic renal disease. Attempts have been made to clarify these risks in the settings of chronic renal insufficiency, dialysis, and transplanted kidneys. Chronic renal disease can be silent until advanced stages. As obstetricians routinely examine the patient’s urine for presence of protein, glucose and ketones, they may be the first to detect chronic renal disease. The effect of pregnancy-related changes in women with preexisting renal disease depends on the type of renal impairment and complications such as hypertension, proteinuria and infection. Advice to women with renal impairment regarding pregnancy must take into account all these parameters in an effort to answer the two most important questions:

- What effect will the pregnancy have on the mother’s kidney disease?
- What effect will the mother’s kidney disease have on the pregnancy?

The features that are detrimental to long-term maternal renal function and pregnancy outcome are:

- The impaired renal function (preconception SCr > 177 μmol/L (2.00 mg/dL) or glomerular filtration rate (GRF) < 25 mL/min) will lead in 2/3 of mothers to have an accelerated decline in renal function and one third to develop End-Stage Renal Failure (ESRF) in association with pregnancy. There is also considerable risk for preterm labor, intrauterine growth restriction (IUGR) and preeclampsia
- Hypertension increases risk of preeclampsia, IUGR, preterm labor and can accelerate the decline of maternal renal function
- Proteinuria in nephritic levels is associated with maternal thromboembolism, IUGR, preterm labor and poorer long-term maternal renal prognosis
- Reduced plasma volume with IUGR
- Hyperglycemia leads to large-for-gestational-age babies, but when associated with microvascular disease there is increased risk of IUGR

Although fertility is diminished in chronic kidney disease (CKD), even women on dialysis may in rare instances become pregnant. Most women will experience an increase of blood pressure and proteinuria and decrease of GRF, which can be irreversible. Affected women are at increased risk of fetal loss, intrauterine growth retardation, and early labor, especially if they experience an acute onset of kidney disease, nephritic syndrome, or hypertension. Additionally, high maternal blood urea nitrogen levels can act as an osmotic diuretic in the fetal kidney and can cause early labor and fetal loss. Progression of the underlying maternal disease depends less on the specific disease than on its severity.
One third of women with moderate kidney disease (GFR < 70 mL/min or serum creatinine > 1.4 mg/dL) are at risk for more rapid declines of renal function than are patients with less severe CKD. Dilated afferent arterioles associated with hypertension in pregnancy can further increase the already elevated intraglomerular pressures. If kidney function deteriorates quickly in early pregnancy, especially with no apparent diagnosis, renal biopsy should be considered and can be performed safely. According to Katz, 85% of women with chronic renal disease will have a surviving infant if renal function is well preserved, earlier reports being more pessimistic [Katz, 1980]. Many studies underlined that if there isn’t a good control of the blood pressure there is a high likelihood of pregnancy loss. Developing of the antepartum fetal surveillance and advances in neonatal care have improved the perinatal outcome. Hou and collaborators reported a 13.8% of fetal loss rate, including miscarriage, stillbirths and neonatal deaths, this percent being close to the general population’s one [Hou, 1999]. Holley and collaborators appreciated that early pregnancies losses are more common in patients with preexisting renal disease [Holley, 1996]. Higher rates of preterm delivery and IUGR were observed in women with normal or near normal renal function and mild to moderate renal impairment. Preexisting severe renal impairment (SCr > 220 umol/L) is associated with more preterm deliveries and lower birth weights than a lower SCr. A higher rate of cesarean section is seen in these women and older studies, before 1995, the perinatal outcome was good. Most authors agreed that it is difficult to assess the independent contribution to poor fetal outcome of maternal hypertension, proteinuria and renal impairment. The balance of evidence suggested that each parameter is individually and cumulative detrimental to fetal outcome. A blood pressure higher than 140/90 mmHg in the context of chronic renal disease leads to a fetal mortality of ~23%, 6 times higher than in normal population. Treatment of maternal hypertension in pregnancy is also challenging because only few classes of antihypertensive drugs are permitted in pregnancy: methyldopa, labetolol, nifedipine, or alpha antagonists. A study showed that increased proteinuria in pregnancy is associated with decreased infant weight. The risk of thromboembolism is also higher in pregnant women with nephrotic syndrome. The authors still have controversy on administration of prophylactic low-dose aspirin during pregnancy in attempt to prevent glomerular capillary thrombi, preserve maternal renal function and reduce the risk of preeclampsia [Katz, 1980; Barcello, 1986; Coomarasamy, 2003].

4. Specific renal diseases in pregnancy

Glomerular diseases such as membrane-proliferative glomerulonephritis, focal glomerulosclerosis, and reflux nephropathy were associated with poorer renal outcomes. In addition, pregnant women with autosomal dominant polycystic kidney disease that are hypertensive have a high risk for fetal and maternal complications, but women who are normotensive with mild kidney disease usually have uncomplicated pregnancies. In women with systemic lupus erythematosus, the best outcomes occur in stables inactive lupus for 6 months or longer before conception. Usually renal flares in pregnancy associated with proteinuria, hypertension, and decreased GFR, makes the distinction from preeclampsia very difficult. However, low complement levels may be helpful in distinguishing between women with preeclampsia and those with active lupus nephritis. All these women should be screened for anti-SSA (Ro) antibodies, due to the risk of congenital heart block. Treatment is difficult because usually used drugs in lupus therapy like cyclophosphamide and
Renal Disease and Pregnancy

mycophenolate mofetil are potentially teratogenic in early pregnancy. Pregnant women with diabetic nephropathy may also develop proteinuria and hypertension.

4.1 Preeclampsia
Preeclampsia rarely causes acute renal failure severe enough to require dialysis. Acute renal failure (ARF) has become a rare complication of pregnancy in developed countries [Prakash, 2006]. Studies show that temporary dialysis was needed in hemorrhage due to placental abruption or HELLP syndrome. Women with preexisting renal disease as presented before are more vulnerable to preeclampsia, a higher risk population being that with chronic hypertension. A meta-analysis of trials investigating the effectiveness of low-dose aspirin administration (50-150 mg/day) in pregnant women with moderate to severe renal disease revealed significant reduction in the risk of preeclampsia and perinatal death [Drakely, 2002]. Delivery of the baby and placenta is the cure of severe preeclampsia. This will halt the general progression of preeclampsia, but postpartum maternal renal function usually deteriorates before improving [Rosenne-Montella, 2008]. Dialysis is limited to few cases, HELLP syndrome or placental abruption and SCr doubled in 24-48 hours, being such cases. Fluid balance is essential in the management of ARF in pregnancy, as well as the control of hypertension.

4.2 Primary glomerulonephritis
Acute primary glomerular disease rarely coincides with pregnancy. Barnes, from all available records observed a fetal salvage of only 43 600 and a maternal mortality of 20-25% during pregnancy but made it clear that such statistics would be improved with modern treatment [Barnes, 1970]. Self-limited glomerular disease preceding pregnancy has, however, no adverse effects [Tillman, 1951; Felding, 1968]. Chronic glomerular diseases, mainly on account of their diverse pathogenesis, have a less clear-cut relationship to pregnancy. Some are more progressive than others, their courses often punctuated by remissions and relapses. An established proteinuria before pregnancy may worse during it, considering increased GRF. Augmented by salt and water retention, it may produce a full nephrotic syndrome. However, assuming the edema is adequately controlled by diuretics and that neither hypertension nor renal failures supervene, the outlook for both mother and fetus is good. Several studies sustained this idea. In 1963, Johnston and collaborators studied 29 pregnancies in 10 patients with nephrosis (uncomplicated in five cases and complicated in five cases). In 1969, Studd and Blainey recorded only two infant deaths in 31 nephrotic pregnant women. In uncomplicated group were registered 11 live births from 12 pregnancies and in complicated group were 2 miscarriages, six abortion and only nine successful deliveries. In a 10-year follow up of 23 nephrotic patients involving 35 pregnancies were recorded 33 normal deliveries although infant weights were reduced relative to their maturities [Blainey, 1971]. Only two mothers with severe proliferative glomerulonephritis showed serious deterioration of renal function requiring dialysis or transplantation. In another study of 41 pregnancies in 25 patients whose renal diseases had been defined by renal biopsy were obtained favourable results [Strauch, 1974].

4.3 Lupus nephritis in pregnancy
Glomerulopathies form an important aspect of several systemic diseases of which systemic lupus erythematosus (SLE) is one of the more important. About 50% of women with this
disease experience renal involvement in a wide variety of forms which may range from a focal proliferative glomerulonephritis to a more indolent and diffuse thickening of glomerular basement membranes. This variety of glomerular involvement, together with changing treatment over the years, accounted for some of the controversy which surrounds its relationship to pregnancy. 20 years ago, women with systemic lupus erythematosus (SLE) were advised against pregnancy due to fear of irreversible consequences for the mother. Today the advent of combined teams of obstetricians and ‘lupus doctors’ offering coordinated care for both, the mother and the baby improved significantly these terms [Ruiz-Irastorza, 2009]. The fertility rate in women with SLE is relatively normal compared to the general population; however, fetuses born to mothers with SLE may face major complications [Mok, 2001]. Multiple adverse pregnancies such as fetal loss, preterm birth, and pre-eclampsia are associated with SLE. The risk is caused by the ability of maternal autoantibodies to cross the placenta and initiate pathogenesis of the fetus. One of the most severe SLE-associated conditions is the formation of congenital heart block and can develop as a result of the passage of maternal autoantibodies. A lot of researchers studied the interrelationship of pregnancy and SLE and concluded that a great number of complications are possible in pregnant women with SLE. The presence of proteinuria, thrombocytopenia and arterial hypertension in the first semester in pregnant mother with SLE are major risks factors for pregnancy loss. The women with such risk factors have a probability of pregnancy loss of 30-40% [Clowse, 2006]. A study performed in United States from 2000-2003, compared maternal and pregnancy complications for all pregnancy-related admissions for women with and without systemic lupus erythematosus. Of more than 16.7 million admissions for childbirth over the 4 years, 13,555 were to women with systemic lupus erythematosus. The study related a maternal mortality of 20-fold higher among women with systemic lupus erythematos [Clowse, 2008]. Different signs and symptoms of pregnancy may easily be confused with signs of active lupus. Symptoms such as fatigue, melasma, palmar erythema and facial hair in the postpartum dyspnea, arthralgia, and headache are frequent in a normal pregnancy. Arthralgias are common among pregnant women due to increased weight as well as the effect of relaxin on the joints [Clowse, 2007]. A complete set of auto-antibodies should be done in every pregnant women with SLE, especially anti-phospholipid antibodies (aPL), both anti-cardiolipin antibodies (aCL) and lupus anticoagulant (LA) and anti-Ro and anti-La antibodies, given their close link with specific pregnancy complications (thrombosis, embryo/fetal loss, pre-eclampsia and congenital heart block) [Ruiz-Irastorza, 2009]. During pregnancy, C_{3} and C_{4} may be elevated, though a flare may occur despite apparently normal levels. However, a decrease of C_{3} or C_{4} levels by more than 25% may be considered an indicator of disease activity [Buyon 1999]. Lymphopenia, but not leucopenia, should be considered an indicator of SLE activity in pregnancy, because a neutrophil leucocytosis can occur in the third trimester [Motha, 2009]. Elevated uric acid levels indicates toxemia, while the presence of hematuria and/or cellular casts, extrarenale activity, elevated anti-DNA antibody levels, and decreased complement levels indicate lupus nephritis [Mackillop, 2007]. The treatment in pregnant with SLE is based on hydroxychloroquine, low-dose steroids, azathioprine and in patients with anti-phospholipid antibodies, low-dose aspirin ± low molecular weight heparin. It is recommended a close surveillance, with monitoring of blood pressure, proteinuria and placental blood flow by Doppler studies [Ruiz-Irastorza, 2009]. Maintenance of the autoantibody levels in the mother’s blood is essential and a key method in sustaining the
health of the fetus by preventing the likelihood of maternal-fetal exchange of SLE-associated autoantibodies. Another major contributor to adverse SLE pregnancy outcomes is antiphospholipid syndrome (APS), defined as the presence of an antiphospholipid antibody (APL) in association with clinic features of venous/arterial thrombosis or specific pregnancy complications [Smith, 2009]. Optimal management is not over with the birth of a healthy baby. Postnatal maternal monitoring by a nephrologist is indicated for optimization of hypertension and lupus nephritis treatment, without concerns for medication-related fetal adverse effects. A close surveillance in the first 4 weeks after delivery is warranted, especially in women with recent activity or previous severe disease. However, no specific prophylactic therapy (such as increasing the dose of steroids) is recommended [Ruiz-Irastorza, 2009].

4.4 Urinary tract infections and pyelonephritis in pregnancy

Urinary tract infections (UTIs) are one of the most common medical complications of pregnancy [Berard, 2011]. It is estimated that one in three women of childbearing age will have a UTI [Duarte, 2008]. The incidence of asymptomatic bacteriuria is 2% to 10%, which is the same during pregnancy as it is in sexually active nonpregnant women [Hooton, 2000]. However, the structural and immune changes the urothelium of the renal tract in pregnancy make it more likely that a lower UTI will ascend to cause acute pyelonephritis. Studies mention that between 12.5% and 30% of patients with untreated asymptomatic bacteriuria will develop acute pyelonephritis, causing significant morbidity to both mother and fetus [Little, 1966; Nowicki, 2000]. The most common uropathogens are: Escherichia Coli (70-80%), Klebsiella, Proteus, Enterobacter and Staphylococcus saprophyticus. Asymptomatic bacteriuria beside its risk to progress to acute pyelonephritis as mentioned has a high recurrence risk, and is also associated with increased risk for preterm delivery and low birth weight [Tincello, 1998]. Although controversial modern literature doesn’t advice for asymptomatic bacteriuria screening unless the population has a prevalence of more than 5% (usually the prevalence is ~2.5%), or in particular cases with history of frequent urinary infection, or other subsequent risk factors for urinary infection. Treatment of asymptomatic bacteriuria should take into account that the most frequent agent causing it is Escherichia Coli. Patients can therefore be safely treated with nitrofurantoin, ampicillin, cephalosporins and short-acting sulfa drugs. Therapy should be for 3-7 days and the patient should repeat the urine culture 1 to 2 weeks after finishing the treatment. Aprox 15% will experience reinfection and/or will not respond to the initial therapy [Romero, 1989; Davison, 1989]. Although pyelonephritis affects only 1-2% of pregnant women, it is accompanied by significant maternal morbidity and fetal morbidity and mortality [Gilstrap, 2001]. In 20-30% of pregnant women with pyelonephritis can result premature labor and the babies at high risk of neonatal death [Steer, 2005]. It is the most common non-obstetric cause for hospitalization during pregnancy. It is caused by the same uropathogens that cause asymptomatic bacteriuria. Studies reflect that the screen for asymptomatic bacteriuria in high risk population (history of asymptomatic bacteriuria, previous recurrent UTIs, preexisting renal disease- especially scared kidneys due to reflux nephropathy, structural and neurophatic abnormalities of the renal tract, renal calculi, preexisting diabetes mellitus-but not gestational diabetes, sickle cell disease, low socioeconomic group and less than 12 years higher education)decreases the risk for acute pyelonephritis to less than 1% [Plattner, 1994]. Most women will present pyelonephritis in the second or third trimester of pregnancy.
and will accuse in over 80% of cases: backache, fever, rigors, and costovertebral angle tenderness, and about half have lower urinary tract symptoms, nausea and vomiting. Bacteremia is present in 15% to 20% and only very few will develop septic shock or more severe complications. High risk cases will present: highest fever (> 39.4 degrees C), tachycardia (>110 bpm) [Cunningham, 1987]. Acute pyelonephritis can trigger uterine contractions and preterm labour, so the tocolytic therapy should be used carefully if there are cervical changes. Pregnant women suspected of acute pyelonephritis should be admitted in hospital for treatment. Those presenting in shock need to be referred to the intensive care unit. The treatment is empiric first, with intravenous antibiotic until sensitivities of blood and urine cultures are known. Usually these patients associate a degree of renal impairment, thrombocytopenia, and hemolysis, suggesting that alveolar capillary endothelium is damaged by endotoxin [Winf, 2001]. As the Gram-Negative bacteria usually causing pyelonephritis are often resistant to ampicillin the first choice of antibiotics should be intravenous cephalosporins, such as cefuroxime 750 mg to 1.5 g every 8 hours, until cultures results are known. Gentamicin can also be used. Intravenous antibiotics should be used until the patient is afebrile for 24 hours, and then the treatment should be followed by oral antibiotics for 7-10 days, as if for lower urinary infections. Following one episode of acute pyelonephritis, the pregnant woman should have monthly urine cultures for the recurrence screen [Dunlow, 1990].

4.5 Acute renal failure and renal cortical necrosis in pregnancy

Acute renal failure in pregnancy is largely a preventable problem usually resulting from obstetric complications and not intrinsic renal disease. With this in mind, pregnancy related acute renal failure (ARF) can be viewed more as a public health problem than a nephrologic problem [Hou, 1998]. Acute renal failure (ARF) represents a plurietiological syndrome characterized by the kidney incapacity to clear the metabolism products of the organisms. It is a very severe condition, fortunately rare in nowadays. Acute renal failure (ARF) and septic abortion is the most frequent form of ARF in early pregnancy especially in developing countries, where pronatality policies forbidden abortion. Such a case was also in Romania during the communist regime (in the seventies and eighties) when the maternal mortality got to ~ 500-600/100000 women. ARF appears due to the severe toxico-infectious syndrome (usually caused by anaerob bacteria- Clostridium velchii) after an abortive maneuver. Renal injuries are represented by acute tubular necrosis, and in very severe cases cortical bilateral necrosis. Evolution is characterized by initial oligoanuria followed by septicemic signs. Treatment addresses the primary septicemic reservoir (hysterectomy, massive antibiotherapy), dialysis. Global mortality I this pathology remain at high levels ~15-20%.

Around the time of delivery, ARF is commonly caused by gestational syndromes such as preeclampsia/hemolysis, elevated liver enzymes and low platelets (HELLP syndrome) and abruption placenta [Spargo, 1959; Redman, 1999; Poston, 2002]. ARF multiple etiologies recognize common causes such as: urinary tract infections (especially acute pyelonephritis), intoxications with drugs or nephrotoxic substances, septicemic states, shock, major hidroelectrolitic disequilibrium, posttransfusion accidents, urological causes (lithiasis, tuberculosis, ureteral obstructions). Specific etiological factors connected to the pregnancy status are: placental abruption, severe preeclampsia/HELLP syndrome, septic abortion, hyperemesis gravidarum, ovarian hyperstimulation syndrome, amniotic fluid embolus, hemolytic uremic syndrome/ thrombotic thrombocytopenic purpura, acute fatty liver of pregnancy and acute
obstruction of real tracts. The most common renal lesion is acute tubular necrosis and cortical necrosis usually appears in non pregnant patients. Positive diagnosis of ARF is based on oligoanury (less than 100 ml urine/24 hours) and association of uremic retention, hypercalcemia, hypermagnesemia, metabolic acidosis. ARF is a severe complication that triggers other complications: infectious (pneumopathy, thromboembolism, parotiditis), hidroelectrolitical (edema, hypertension, congestive cardiac failure), hemorrhagical. Treatment of ARF concentrates on finding the cause and treat it dialysis has more indications nowadays. The obstetric management of the patient has to take into account the gestational age and the fact that pregnancy related acute renal failure has a more severe evolution and prognosis than other causes.

Acute renal cortical necrosis is a rare complication of pregnancy nowadays. In western countries, the frequency of renal cortical necrosis range from 1.9% to 2% [Schreiner, 1979]. Obstetric complications such as abruptio placentae, septic abortion, eclamptic toxemia, post-partum hemorrhage, intrauterine fetal demise, amniotic fluid embolism and puerperal sepsis can cause renal cortical necrosis [Ali, 2003]. By all, the most common obstetric cause is abruptio placentae, responsible for 50-60% of cases [Jeong, 2002]. Acute renal cortical necrosis should be suspected if anuria persists. Definitive diagnosis can be made only by renal biopsy. Incidence of maternal and fetal mortality is still increased [Chugh, 1994].

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are very similar syndromes characterized by microangiopathic hemolytic anemia and thrombocytopenia. They appear more likely in the third trimester of pregnancy and determine a multiorgan disorder, women with these pathology present gastrointestinal or neurological abnormalities. Maternal survival from HUS/TTP has greatly improved since treatment with plasmapheresis [Greer, 2007]. Steroids are often added to the plasma exchange, but there are no randomized controlled trials of their use [Rosene-Montella, 2008]. Antiplatelet regimen with aspirin may also be beneficial [McMinn, 2001].

4.6 Diabetic nephropathy in pregnancy
In the last 10 years an increased number of people with type 2 diabetes mellitus appeared. Diabetes mellitus (DM) is the most common medical complication of pregnancy and it carries a significant risk to the fetus and the mother [Abourawi, 2006]. Gestational DM represents approximately 90% of these cases and affects 2-5% of all pregnancies and varies in direct proportion to type 2 diabetes mellitus in the background population [Ben-Haroush, 2004]. There is a clear association between obesity and adverse pregnancy outcomes (cesarean section, gestational diabetes, hypertensive disorders, birth defects and prematurity) [McIntyre, 2009]. Pregnant women with diabetes are at risk of progression to microvascular diabetic complications, early pregnancy loss, pre-eclampsia, polyhydramnios and premature labour. Glycemic control before and during pregnancy is critical and the benefit may result in a viable, healthy off spring [Hertzel, 2001]. The risk of neonatal macrosomia and hypoglycemia can be reduced by proper management of gestational DM. Appropriate counseling in women with gestational DM and post-partum evaluation of glucose tolerance may help decrease the high risk of subsequent type 2 diabetes in the long-term [Kitzmiller, 2007]. Metabolic changes occur in normal pregnancy in response to the increase in nutrient needs of the fetus and the mother. There are two main changes which are seen during pregnancy, progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to the level that approximates the insulin
resistance seen in individuals with type 2 diabetes mellitus [Abourawi, 2006]. The insulin resistance appears to result from a combination of increased maternal adiposity and the placental secretion of hormones (progesterone, cortisol, placental lactogen, prolactin and growth hormone). The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. The second change is the compensatory increase in insulin secretion by the pancreatic beta-cells to overcome the insulin resistance of pregnancy [Ben-Ziv, 2008]. Circulating glucose levels are maintained normal. If there is maternal defect in insulin secretion and in glucose utilization, then GDM will occur as the diabetogenic hormones rise to their peak levels. Maternal diabetes complications are frequent in women with both type 1 and type 2 diabetes [Abourawi, 2006]. Diabetic retinopathy and diabetic nephropathy may progress or start de novo during the pregnancy.

Diabetic pregnant woman can have maternal complications such as: diabetic ketoacidosis, hypoglycemia, and retinopathy, deterioration of nephropathy, vomiting (gastric neuropathy), miscarriages, preeclampsia, polyhydramnios, and premature delivery. In order that diabetic pregnant women have a healthy baby and avoid maternal morbidity it is recommended a multidisciplinary pre-pregnancy consult. Ideally this is carried out by a team, which includes an obstetrician, a nephrologist and a diabetologist for optimum care. Clinical trials of pre-conception care to achieve stringent blood glucose control in the pre-conception period and during the first trimester of pregnancy have demonstrated striking reductions in rates of malformation compared with infants of diabetic women who did not participate in pre-conception care [Ray, 2001]. In approximately two thirds of women with diabetes, may appear pregnancy, without an adequate pre-conception care and a lot of malformations in their infants. Oral hypoglycemic agents should be interrupted before pregnancy and insulin started if needed, and also statins and ACE-inhibitors should be discontinued. Safer drugs like Methyldopa, Nifedipine or Labetalol should be administered for arterial hypertension. It is necessary be evaluated and treated all the diabetic complications. Regular self-monitoring should be encouraged to optimize control. At least at four weeks pre-conception it should be administered Folic acid. Glycemic control should be optimized with the aim of pre-prandial blood glucose < 5.5 mmol/l (< 95 mg/dl) and HbA1c < 7%. Home blood glucose monitoring is an essential part of maintaining euglycemic state and its goal is to detect glucose concentration to allow fine-tuning of insulin adjustment, pre-prandial glucose level < 5.5 mmol/l (< 95mg/dl), and postprandial level glucose < 7.8 mmol/ l (<140 mg/dl). Post-prandial glucose levels have been shown to correlate more with macrosomia than do fasting levels. Diabetes in early pregnancy studies found that third trimester post-prandial glucose levels were the strongest predictors of percentile birth weight [Setji, 2005]. Diet in pregnancy should provide an adequate nutrition for both mother and fetus, with sufficient calories for appropriate maternal weight gain, for maintaining normal glycemia and avoiding ketosis. It is recommended that pregnant women with diabetes to eat three small to moderate size meals and three snacks per day. Monitoring with a pre-breakfast ketone measurement is recommended for patients who are on a hypo-caloric or carbohydrate restricted diet [Franz, 2002]. Before conception, a baseline assessment of renal function by serum creatinine and some measure of urinary protein excretion (urine albumin/creatinine ratio or 24-hour albumin excretion) should be done. Women with microalbuminuria may experience transient worsening during pregnancy; however, those with established nephropathy with overt proteinuria are at increased risk of
pre-eclampsia and intra-uterine growth retardation and premature delivery [Abourawi, 2006]. A frequent associated pathology of diabetes is arterial hypertension. Patients with type 1 diabetes frequently develop hypertension in association with diabetic nephropathy, as manifested by the presence of overt proteinuria. Patients with type 2 diabetes more commonly have hypertension as a concomitant disease. In addition, pregnancy induced hypertension is a potential problem for the women with diabetes. In pregnancy, arterial hypertension may worse diabetic nephropathy and retinopathy. ACE-inhibitors, beta-blockers and diuretics should be avoided in women contemplating pregnancy if are used for hypertension. Methyl-Dopa or Labetalol should be substituted. Considering the earlier studies in this domain [Purdy, 1996; Reece, 1998; Ekbom, 2001; Rossing, 2002], the management of diabetic nephropathy should follow:

- **Prepregnancy**: advise that pregnancy with diabetic nephropathy and SCr > 124 μmol/L is associated with 40% risk of gestational decline in renal function; advise that increase risk of adverse pregnancy outcome; try and achieve euglycemia
- **Prenatal**: every 4-6 week monitor blood pressure, blood urea nitrogen, glucose, midstream urinalysis until 24 week of gestation, then every 2 week until 32 weeks of pregnancy and after that weekly; try and achieve euglycemia; give aspirin 75 mg once daily to reduce the risk of preeclampsia, control hypertension to < 140/90 mmHg; screen for preeclampsia; fetal surveillance; give LMW heparin when > 1-3 g proteinuria/24 hour and hypoalbuminemia; a diuretic may be necessary for symptomatic relief of gross edema with nephrotic syndrome
- **Postnatal**: reassess the renal function (GFR) postpartum

Treatment with medical nutrition therapy, close monitoring of glucose levels, and insulin therapy if glucose levels are above goal can help to reduce these complications [Setji, 2005].

### 4.7 Unique surgical kidney and pregnancy

Women undergoing nephrectomy (despite the cause of the surgical procedure) will have a pregnancy evolution in normal parameters if the remaining kidney has its morph functional integrity. Multidrug resistant urinary infection can be an indication for ending the pregnancy in order to preserve the renal function. Authors consider that pregnancy won’t influence the renal function and evolution of the renal disease if the blood pressure can be controlled and urinary infection treated promptly if they appear.

### 4.8 Renal calculi and pregnancy

Renal calculi, congenital renal tract abnormalities or a gestational overdistension syndrome can produce renal obstruction in pregnancy [Rosene-Montella, 2008]. The incidence of renal calculi in pregnant women appears to be no greater than in the nonpregnant population. Their presence and especially their migration in the urinary tract are associated with renal colic, UTI. Treatment and management of renal colic is similar as for nonpregnant women. Women born with congenital obstructive uropathies are at increased risk for urine outflow obstruction in second trimester of pregnancy and also for recurrent UTI [Meyers, 1985]. Overdistension of urinary tracts isn’t very frequent in pregnancy. The patients will present severe loin pain, most commonly on the right part and radiating to the lower abdomen. Spontaneous rupture of the kidney is uncommon, and in severe cases ureteric stent or nephrostomy is performed.
4.9 Acute fatty liver of pregnancy

Acute fatty liver of pregnancy was first described in 1940 by H. L. Sheehan as an "acute yellow atrophy" of the liver. Acute renal failure due to acute fatty liver of pregnancy is a rare life-threatening complication, specific to pregnancy. If unrecognized or untreated, the disorder may progress to fulminant hepatic failure with jaundice, encephalopathy, disseminated intravascular coagulation, uncontrollable gastrointestinal and uterine bleeding, and death [Kaplan, 1994]. Although the exact pathogenesis is unknown, it seems to be caused by a disordered metabolism of fatty acids by mitochondria in the mother, caused by deficiency in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase enzyme [Bellig, 2004]. Acute fatty liver of pregnancy may be confused with acute hepatitis or toxemia on both clinical and histological grounds [Burroughs, 1982]. The diagnosis of acute fatty liver of pregnancy is suggested by jaundice with a lesser elevation of liver enzymes, elevated white blood cell count, disseminated intravascular coagulation, and a clinically unwell patient [Riely, 1999]. Usually such patients will present with nausea, vomiting, and abdominal cramps. First appear an impaired renal function and reduced plasma antithrombin levels, liver dysfunction following this [Castro, 1999]. Maternal renal impairment is aggravated by hypotension secondary to hemorrhage, which it is most likely to follow an emergency cesarean section. Renal dysfunction, hemorrhage, and disseminated intravascular coagulation secondary to liver failure require a complex intensive therapy in a multidisciplinary team. Treatment includes supportive care in order to maintain adequate fluid balance for renal perfusion, replacing blood, correcting the coagulopathy. Temporary dialysis might be necessary [Pereira, 1997].

4.10 Pregnancy in women on dialysis

End-stage renal disease requiring dialysis is associated with a marked decrease in fertility. Pregnancy occurs in approximately 1% of women, usually within the first few years of starting dialysis. The cause of infertility is not entirely clear, but it is probably multifactorial. An estimated 42% of women receiving dialysis who are of childbearing age have regular menses, but many more are likely anovulatory. Anemia probably also plays a role. In fact, some investigators suggest that the regular use of erythropoietin improves the pregnancy rate. Generally pregnancy is a contraindication in women on dialysis. The fetal outcome is quite poor. Only 23-55% of pregnancies result in surviving infants, and a large number of second-trimester spontaneous abortions occur. In addition, surviving infants have significant morbidities. Approximately 85% of surviving infants are born premature, and 28% are born small for gestational age. Maternal complications occur as well, including reports of several maternal deaths. Hypertension worsens in more than 80% of pregnant females on dialysis and is a major concern. The diagnosis of pregnancy in these patients is also difficult, because levels of beta-human chorionic gonadotropin (beta-hCG) are normally elevated in patients receiving dialysis. If pregnancy is considered likely and the beta-hCG level is high, obtain an ultrasonogram to aid in diagnosis. Some general recommendations apply to patients who become pregnant while receiving dialysis. Place the patient on a transplant list (if not on already), because outcomes with allograft transplant patients are markedly better. During hemodialysis, pursue uterine and fetal monitoring and make every attempt to avoid dialysis-induced hypotension. Some evidence indicates that judicious use of erythropoietin may improve fetal survival; however, no findings from randomized studies support this. Erythropoietin can also increase hypertension and
must be used cautiously. An increased frequency of dialysis may improve mortality and morbidity. Aggressive dialysis to keep blood urea nitrogen levels less than 50 mg/dL may be pursued with daily dialysis. Controlling uremia in this fashion may avoid polyhydramnios, control hypertension, and improve the mother's nutritional status [Hou, 1998; Holley, 2003].

4.1.1 Pregnancy after renal transplantation

The first reported successful pregnancy occurred in a recipient of a kidney transplant from an identical twin sister performed in 1958 [Murray, 1963]. Fertility is usually restored in women with renal transplants. Pregnancy is then common, occurring in 12% of women at childbearing age in one series [Sturgiss, 1992]. Pregnancy success rates are also quite good, with more than 90% fetal survival rates after the first trimester. Pregnancy can be anticipated, planned, and even encouraged. In patients with chronic renal insufficiency, factors such as uncontrolled or worsening hypertension, worsening proteinuria, and poor prepregnancy renal function are important prognostic indicators for the risk of renal function deterioration. Whether pregnancy itself induces a significant risk to the transplanted kidney's function is unclear. Obstruction of the transplant ureter by the pregnant uterus is quite rare but has been reported. Further long-term studies are indicated. Current opinion holds that the graft function is not adversely affected by pregnancy in the setting of women with a creatinine level of less than 1.4 mg/dL who are treated with prednisone and/or azathioprine. An elevated prepregnancy creatinine level (> 1.4 mg/dL) is associated with a higher risk of renal decline but also with a decreased fetal survival rate. The fetal survival rate is approximately 74% in patients with a creatinine level of more than 1.4 mg/dL, whereas it increases to about 96% in patients with a creatinine level of less than 1.4 mg/dL [EBPG Expert Group on Renal Transplantation, 2002; Davison, 1995].

5. Conclusion

In pregnancy associated with different renal diseases, laboratory tests play an important role. Pregnant women with any renal disease must be prepregnancy counseled, prenatal monitored, and receive a skilled obstetric management in a multidisciplinary manner, since the most common cause of mortality and morbidity in these cases is preterm labor.

6. References


Clinical nephrology is an evolving specialty in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

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