A best practice position statement on pregnancy in chronic kidney disease: the Italian Study Group on Kidney and Pregnancy

Gianfranca Cabiddu · Santina Castellino · Giuseppe Gernone · Domenico Santoro · Gabriella Moroni · Michele Giannattasio · Gina Gregorini · Franca Giacchino · Rossella Attini · Valentina Loi · Monica Limardo · Linda Gammarelli · Tullia Todros · Giorgina Barbara Piccoli

Received: 17 December 2015 / Accepted: 8 February 2016 / Published online: 17 March 2016
© Italian Society of Nephrology 2016

Abstract Pregnancy is increasingly undertaken in patients with chronic kidney disease (CKD) and, conversely, CKD is increasingly diagnosed in pregnancy: up to 3% of pregnancies are estimated to be complicated by CKD. The heterogeneity of CKD (accounting for stage, hypertension and proteinuria) and the rarity of several kidney diseases make risk assessment difficult and therapeutic strategies are often based upon scattered experiences and small series. In this setting, the aim of this position statement of the Kidney and Pregnancy Study Group of the Italian Society of Nephrology is to review the literature, and discuss the experience in the clinical management of CKD in pregnancy. CKD is associated with an increased risk for adverse pregnancy-related outcomes since its early stage, also in the absence of hypertension and proteinuria, thus supporting the need for a multidisciplinary follow-up in all CKD patients. CKD stage, hypertension and proteinuria are interrelated, but they are also independent risk factors for adverse pregnancy-related outcomes. Among the different kidney diseases, patients with glomerulonephritis and immunologic diseases are at higher risk of developing or increasing proteinuria and hypertension, a picture often difficult to differentiate from preeclampsia. The risk is higher in active immunologic diseases, and in those cases that are detected or flare up during pregnancy. Referral to tertiary care centres for multidisciplinary follow-up and tailored approaches are warranted. The risk of maternal death is, almost exclusively, reported in systemic lupus erythematosus and vasculitis, which share with diabetic nephropathy an increased risk for perinatal death of the babies. Conversely, patients with kidney malformation, autosomal-dominant polycystic kidney disease, stone disease, and previous upper urinary tract infections are at higher risk for renal function are differently reported, but are higher in advanced CKD. Strict follow-up is needed, also to identify the best balance between maternal and foetal risks. The need for further multicentre studies is underlined.
Keywords Chronic kidney disease · Evidence based medicine · Pregnancy · Hypertension · Proteinuria · Preeclampsia · Pre-term delivery

Introduction

In 1975, an editorial in the Lancet, entitled Pregnancy and Renal Disease, started with the following sentence: *Children of women with renal disease used to be born dangerously or not at all—not at all if their doctors had their way* [1]. The paper reviewed the previous grim evidence, with minimal chances of a positive outcome for children whose mothers started pregnancy with blood urea nitrogen (BUN) levels higher than 60 mg/dl and with hypertension. In spite of several negative reports, however, the authors gave space to new more positive data and concluded discussing the advice to be given to a woman with chronic kidney disease (CKD) who wants to undertake a pregnancy. The conclusions are still valid in our era of patient empowerment: *the woman should be told that there is a considerable risk to her infant and a small risk to herself, but dogmatic prohibitions do not seem justified today*. Instead, *obstetrician and physician must batter down the hatches and prepare to ride out the storm together with those determined to set sail* [1].

Many of the issues raised in 1975, notably the role of hypertension and proteinuria, the severity of CKD and the presence of specific diseases such as systemic lupus erythematosus (SLE) or autosomal dominant polycystic kidney disease (ADPKD), are still a matter of discussion. However, the context has changed throughout the decades, for several reasons including advances in maternal–foetal care, with a progressive expansion of the foetal viability zone to 22–24 weeks [2–4]. The progressive empowerment of patients with chronic diseases has shifted the attitude from a paternalistic protection of the mother to a shared choice. Meanwhile, the almost unexpected results of pregnancy on dialysis have highlighted the potentials of pregnancy even in the latest stages of CKD [5–13].

The definition of CKD, substituting “renal insufficiency” with the broader concept of “chronic kidney disease”, sets the stage for acknowledging a high prevalence of CKD in pregnancy [14–19].

In this context, the *Kidney and Pregnancy Study Group of the Italian Society of Nephrology* undertook the present best practice review, aimed at combining the available evidence with an in-depth discussion on shared experiences and open questions.

Evidence-based medicine and pregnancy in CKD: methodological insights

The evidence on pregnancy in CKD shares several methodological problems with pregnancy in dialysis and, more generally, with pregnancy in rare and/or heterogeneous diseases [13, 19–21].

CKD is an etiquette gathering many different diseases that may differently affect pregnancy. Immunologic nephropathies are at risk of flares during and after pregnancy. Pyelonephritis and renal malformations share an increased risk of urinary tract infections. ADPKD presents complex ethical problems as regards prenatal counselling. Diabetic nephropathy is the only kidney disease associated with a higher risk for non-renal malformations [19–30]. The lack of shared definitions partially impairs the pooling of the data for systematic reviews, an issue that has to be considered during a critical analysis of the results [19–21, 28, 30].

Kidney disease, degree of kidney impairment, hypertension and proteinuria are well known factors in the pathogenesis of pregnancy-related adverse outcomes. Their interactions are complex, and so far not completely elucidated [31–33].

A major issue is kidney function assessment in pregnancy, a situation in which no validated formula exists and the physiologic hyperfiltration may alter CKD staging [34–38].

It is difficult to perform randomised controlled trials (RCTs) in pregnancy, and often these are ethnically unfeasible [39–41]. Hence, our understanding on pregnancy outcomes in CKD patients mainly relies on observational studies, whose quality is not necessarily inferior as compared to RCTs [42–48]. As a consequence of the “physiological” lack of RCTs and of the paucity of large observational studies, we will deal with low levels of recommendation. We will include several not graded suggestions, whose contribution should however not be underestimated [13].

The research strategy on which the present position statement is based represents an updating, at June 2014, of a previous systematic review on CKD and pregnancy, to which we refer the reader for details on the search strategy and on the paper selection modality [20]. The heterogeneity of the literature and the high number of kidney diseases led us to focus on general features and on the main forms of CKD, highlighting the needs for future research. The Italian Study Group on Kidney and Pregnancy has already covered the issue of pregnancy on dialysis [13]. A further position statement will treat pregnancy in kidney-transplanted patients.
Which CKD patient should be considered at “increased risk” for adverse pregnancy-related outcomes?

1. All CKD patients should be considered at increased risk for adverse pregnancy-related outcomes, and followed-up accordingly (strong suggestion; evidence form relatively large reports from few settings).

2. The risks of adverse pregnancy-related outcomes increase in incidence and severity along with the worsening of CKD. Follow-up should be intensified in patients with severe CKD (strong suggestion; evidence from several reports in different settings, CKD stages and/or in different diseases).

3. Proteinuria, hypertension, type 1 diabetes and immunologic diseases are associated with increased risk. Follow-up should be intensified (strong suggestion; evidence from several reports in different settings).

As already mentioned, the definition of kidney disease has changed over time and the current CKD definition, which includes all patients with signs of kidney disease regardless of the kidney function, dates from the beginning of the new millennium [14–20]. Consequently, most of the older studies regarded advanced CKD and few compared early and late CKD stages in the same settings [14–21, 30, 32, 33, 49–60].

The risks for adverse pregnancy-related outcomes increase from the early CKD stages [20, 21, 28–30, 32, 33, 38, 56–59, 62]. Large studies and meta-analyses demonstrate that the risks further increase along with the worsening of the kidney function, up to dialysis [11, 19, 20, 60–66].

The effect of CKD, even with normal renal function, is confirmed by the significant increase in adverse maternal–foetal outcomes, including preeclampsia (PE), pregnancy induced hypertension and pre-term delivery, in three large cohorts of patients who undertook pregnancy after kidney donation [57, 58, 67]. The reasons why women with single kidney (or kidney scars, glomerulonephritis in remission, etc.) with normal renal function, no proteinuria or hypertension should share a higher risk for adverse pregnancy-related outcomes are not elucidated [32, 38, 57, 58, 67].

In such a context, the working group suggests that all patients with CKD should be considered at increased risk for pregnancy-related adverse events and should be followed, whenever possible, by a multidisciplinary team including nephrology and obstetrics staff. Since the risks increase along with the worsening of the renal function, follow-up should be intensified in severe CKD (see further recommendations). For the management of dialysis patients, please refer to the specific position statement [13].

These conclusions are mostly based upon scattered evidence and underline the need for further studies on large cohorts of CKD patients. Such studies are highly encouraged by the study group.

What are the main adverse pregnancy-related outcomes in CKD patients?

1. The risks of maternal death are low, and hardly quantified; they are mainly described in active or flared immunologic diseases, above all in lupus erythematosus (strong suggestion; scattered evidence).

2. The risks of worsening of the kidney function, of developing hypertension and of developing or increasing proteinuria increase along with CKD stage (moderate suggestion; scattered evidence).

3. The foetal risks are mainly related to prematurity (strong suggestion; scattered evidence).

4. Perinatal death may be increased in specific diseases (SLE, immunologic systemic diseases, and diabetic nephropathy) (strong suggestion; scattered evidence).

5. Malformations are not increased in CKD patients, with the possible exception of diabetic nephropathy (strong suggestion, large body of evidence from different sources on non diabetic CKD; one paper only reporting on increase in malformations in diabetic nephropathy).

6. Risks for adverse materno-foetal outcomes may be increased in multiple pregnancies (moderate suggestion, one large series only).

Pregnancy-related outcomes in CKD may be related to the mother and to the foetus–child. The maternal risks are death, and progression of CKD, including also increase in proteinuria, impaired control or onset of hypertension, eventually persisting after delivery. The risks for the foetus–newborn are perinatal death, malformations, preterm-birth, intellectual deficiencies, diseases in adulthood [18–20].

Maternal death is reported as a very low or non quantifiable risk, at least in Western Countries, where maternal mortality is already low at baseline [18–20, 66]. According to most large series and systematic reviews, maternal deaths are almost exclusively reported in patients with systemic immunologic diseases, first of all SLE, also on account of the fact that SLE represents the most common systemic immunologic disease in pregnancy [18–20, 23, 68–70].

The risk for worsening of kidney function may increase along CKD stages; its entity has been differently calculated, from about 20 to over 80%; however, a recent systematic review did not find a higher risk of kidney
function reduction in CKD patients with versus without pregnancy in stages 1–3 [16–21, 25, 49–53, 60, 62, 71].

An increase in proteinuria is common; it is more frequent in patients already proteinuric at start of pregnancy and may be higher in diabetic nephropathy. However, the definition of a “relevant increase” in proteinuria is quite elusive, and the reported prevalence ranges from 20 to almost 100% of the cases [25–29, 72–74].

Prematurity (defined as birth before 37 completed gestational weeks), early preterm delivery (before 34 completed gestational weeks) and extremely preterm delivery (before 28 gestational weeks) are increased in CKD pregnancies and, once more, the risk of preterm delivery, as well as the degree of prematurity, rises across CKD stages [18–21, 52–56].

Prematurity brings several short- and long-term risks for the babies: perinatal death, retinopathy, neurological problems (eventually linked to brain haemorrhage), and a possible long-term increase of hypertension, CKD and cardiovascular diseases [75–90]. The last phases of glomerular formation and maturation occur in late gestation; not surprisingly, therefore, a strong correlation has been described between prematurity, low birth weight, low nephron number, and development of kidney disease in adulthood [75–90].

Children from mothers affected by diabetes and systemic-immunologic diseases have a higher risk of perinatal death, also when born at-term or in the late preterm phase. This risk seems more related to the specific disease than to the degree of renal functional impairment [22, 23, 28, 69, 70]. There is no evidence that children from non diabetic CKD mothers have a higher risk of malformations, beside urinary tract malformations, including vesico-ureteral reflux, and related conditions, that are known to have a genetic background, albeit so far partially understood.

One recent study, on a large series, conversely suggests that the presence of nephropathy increases the risk for malformations in children of diabetic mothers. Several different malformations have been reported, with an odds ratio of 2–3 as compared with mothers without nephropathy [91].

According to one case series and a few case reports, multiple pregnancies may have higher risks of adverse pregnancy related outcomes [92–95]. This should be kept in mind in particular in the case of assisted reproduction techniques.

Very few studies have been specifically addressed at the health status of children from CKD mothers; they analysed different aspects of health, from kidney function to psychological well-being. Within the limits of the scattered evidence, it appears that most of the children from CKD mothers are able to attain normal developmental goals, at any level of kidney function impairment [11, 12, 96–98].

According to the Study Group, there is need for further studies, focusing on the clinical and psychological long-term outcome of children from CKD mothers.

**Indications and goals for follow-up**

1. The main goals of follow-up are early identification and treatment of complications, including hypertension, anaemia, coagulation disorders, and timely planning of delivery (strong recommendation, indirect evidence).
2. Follow-up should be intensified in CKD patients with respect to normal pregnancies (strong recommendation, indirect evidence).
3. Follow-up should be increased along with the increase in CKD stages, and according to the presence of other risk factors, such as hypertension, proteinuria and systemic disease (strong recommendation, indirect evidence).
4. Follow-up should include at least one nephrological visit with blood and urinary tests every 4–6 weeks in non proteinuric, non hypertensive stage 1 CKD pregnancies and should be increased to weekly in intensely proteinuric, hypertensive patients or in CKD stages 4–5 (strong recommendation, indirect evidence).
5. No validated formula for glomerular filtration rate (GFR) calculation in CKD pregnancy is available, hence GFR should be assessed by 24-h urine collection (strong recommendation, based on GFR in normal pregnancy and PE).
6. 24-h protein excretion is preferable for quantification of proteinuria (strong recommendation, indirect evidence).
7. Twice monthly to weekly urinalysis and urinary cultures may be indicated in the prevention of urinary tract infection (UTI) recurrences and for early detection of proteinuria (strong recommendation, evidence limited to one RCT).

Pregnancy is not a disease nor a disease complication; however, it may be complicated by the presence of maternal diseases. Hence, there is no specific “treatment” for pregnancy in CKD, and conversely several therapies that are used in CKD outside of pregnancy are contraindicated in pregnancy (Tables 1, 2, 3, 4). Consequently, the main goals of follow-up are early identification and treatment of potential complications, including hypertension, proteinuria, anaemia, coagulation disorders, and flares of systemic diseases.

In the absence of RCTs, the Study Group suggests to intensify follow-up in CKD patients as compared with...
normal pregnancies, increasing the frequency of visits along with the increase in CKD stages, and according to the presence of hypertension, proteinuria and systemic diseases [21, 32, 52]. The flow charts highlight the proposed minimal frequency of controls (Figs. 1, 2, 3).

The assessment of kidney function in pregnancy is challenging, due to hyperfiltration, and increase in plasma volume and in volume distribution. To date, no formula is validated for GFR calculation in CKD pregnancy, and it is preferable to assess creatinine clearance on 24-h urine collection, at least in patients trained to follow the indications. This also allows a precise assessment of proteinuria [33–38].

The Study Group suggests a minimum requirement of one nephrology visit with blood and urinary tests every 4–6 weeks in non proteinuric, non hypertensive stage 1 CKD pregnancies, increased up to weekly in patients with various combinations of proteinuria, hypertension or CKD stages 4–5. Patients at risk of recurrent UTIs, of immunologic flares or with glomerulonephritis in remission should control urinalysis for proteinuria and/or urinary cultures every 1–2 weeks, to promptly identify UTIs and/or proteinuria (Figs. 1, 2, 3).

### Differential diagnosis between CKD and preeclampsia

1. The differential diagnosis between PE and CKD, and the definition of superimposed PE on CKD may be impossible on clinical grounds (strong recommendation, limited evidence).

2. PE of placental origin is usually associated with impaired utero-placental Doppler flows (strong recommendation, scattered evidence).

3. PE ad CKD may be differentiated by means of the angiogenic-antiangiogenic patterns (soluble Fms-like tyrosine kinase 1 [s-Flt-1], placental growth factor [PIGF]) (medium recommendation, scattered evidence).

| Drug            | Main features                                                                 | FDA   | SOGC |
|-----------------|------------------------------------------------------------------------------|-------|------|
| Alpha-methyldopa | Widely used in pregnancy, with no reported negative effects on the foetus or on its subsequent development. May not be able to correct severe hypertension in CKD | B     | 1-A  |
| Niphedipine     | The long acting drug most commonly used in hypertension in pregnancy. The increase in peripheral oedema may be a relevant side effect in CKD patients | C     | 1-A  |
| Labetalol       | Usually well tolerated, should be avoided in subjects with asthma. In a RCT it was shown to be comparable to alphamethyldopa [143, 149] | C     | 1-A  |

### Table 1 Main anti-hypertensive drugs in pregnant patients with CKD

| Drug            | Main features                                                                 | FDA   | SOGC |
|-----------------|------------------------------------------------------------------------------|-------|------|
| **Usually considered FIRST CHOICE drugs [141, 142, 340, 368]** |                                                                               |       |      |
| Alpha-methyldopa | Widely used in pregnancy, with no reported negative effects on the foetus or on its subsequent development. May not be able to correct severe hypertension in CKD | B     | 1-A  |
| Niphedipine     | The long acting drug most commonly used in hypertension in pregnancy. The increase in peripheral oedema may be a relevant side effect in CKD patients | C     | 1-A  |
| Labetalol       | Usually well tolerated, should be avoided in subjects with asthma. In a RCT it was shown to be comparable to alphamethyldopa [143, 149] | C     | 1-A  |

| **Usually considered SECOND CHOICE drugs [141, 340]** |                                                                               |       |      |
| Beta blockers   | The main drawback in older studies was foetal growth restriction, possibly as an effect of overzealous correction [142]. Beta1 selective beta blockers (atenolol) are more often involved. Beta blockers may be more effective than alpha-methyldopa in severe hypertension, alone or in combined therapy. At delivery they may induce hypoglycaemia, hypotension and bradycardia (usually mild and transient) | D     | 1-B  |
| Clonidine      | The effect is similar to alpha-methyldopa; side effects may be more common and hypertensive rebounds at discontinuation are common; slowing foetal growth is occasionally reported [144] | C     |      |
| Clonidine      | The effect is similar to alpha-methyldopa; side effects may be more common and hypertensive rebounds at discontinuation are common; slowing foetal growth is occasionally reported [144] | C     |      |

| Alpha blockers | Other drugs should be preferred as controlled studies are missing | C     |      |
| Diuretics      | They are usually avoided in pregnancy except when there are nephrological or cardiological indications. Thiazides may be continued in patients previously on treatment [143, 158]. In selected cases with Gitelman syndrome, amiloride may be employed | C     |      |

| **To be avoided [141, 340]** |                                                                               |       |      |
| Short acting niphedipine | Contraindicated by the FDA, RCOG and AIPE due to the risk of severe sudden hypotension with detrimental effects on placental flows | D     |      |
| ACE-i ARB and related drugs | Both drugs are contraindicated in all phases of pregnancy because of the risk of several major malformations, including cardiovascular, central nervous system, renal and bone malformations [153–155] | C     | 1st  |

FDA site of the Food and Drug Administration [340]; FDA rating: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy; SOGC, Society of Obstetrics and Gynaecology of Canada: guidelines 2014 [102].
Kidney biopsy is not recommended in pregnancy, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

| Drug          | Main features                                                                 | FDA   |
|---------------|------------------------------------------------------------------------------|-------|
| Azathioprine  | This is the most widely used immunosuppressive drug. It is teratogenic in animal models, but not in humans, possibly because the foetal liver is not able to activate the drug. K-DIGO and European Best Practice Guidelines suggest switching from Mycophenolate to Azathioprine before pregnancy [341–343] | D     |
| Cyclosporine A| This Calcineurin inhibitor has not been associated with increased teratogenicity; however, small for gestational age babies and preterm delivery have been reported, possibly due to the maternal disease and not specifically to the drug; levels may vary in pregnancy and the hypertensive, hyperglycaemic and nephrotic effects should be mentioned [344] | C     |
| Tacrolimus    | The drug has similar effects and side effects as Cyclosporine A; since it is a relatively new drug, experience is more limited than with the previous drug [345] | C     |
| Steroids      | Together with azathioprine these are the most often employed and best known drugs. The most frequently used short-acting corticosteroids include prednisone, methylprednisolone and prednisolone, while betamethasone and dexamethasone are among the long-acting drugs. No major malformations have been reported, and the issue of labio-palatostichis is debated. A higher risk of premature rupture of membranes has been reported. Other relevant side effects include infectious risk, and the increased risk of gestational diabetes [346] | C     |
| Hydroxychloroquine | This synthetic anti-malaric agent crosses the placenta but was not found to be associated with foetal toxicity [217–219] | B     |
| Cyclophosphamide | This alkylating agent is contraindicated in pregnancy; a few reports suggest that pregnancy termination is common in the case of inadvertent use or need for life saving therapy. A few positive reports, mainly in women with SLE are also available [68] | D     |
| Mycophenolate | Severe foetal malformations are reported, mainly involving cardiovascular and cranial malformations. Discontinuation for at least 6 months, to stabilize kidney function, is usually indicted after kidney transplantation [347, 348] | D     |
| Rituximab     | There are no data on whether rituximab can cause foetal harm. Rituximab was detected postnatally in the serum of infants exposed in utero: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants. The manufacturer recommends contraception for up to 12 months following therapy [369, 370] | C     |
| m-Tor inhibitors | Very few studies have considered their use in pregnancy. They are teratogenic in animals and discontinuation in humans is a matter of debate; K-DIGO guidelines suggest discontinuation in anticipation of pregnancy [347, 349] | C     |

**Table 2 Main immunosuppressive drugs in pregnant CKD patients**

**FDA site of the Food and Drug Administration [340]; FDA rating: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy**

4. Kidney biopsy is not recommended in pregnancy, either for the definition of the kidney disease or for the differential diagnosis between PE and CKD, because of risk of severe complications (strong recommendation, systematic review of scattered evidence).

The broad definition of PE includes both mildly affected subjects, whose situation is compatible with term delivery of “appropriate for gestational age” babies, as well as patients affected by stormy, devastating and even deadly disease, with “small for gestational age” (SGA) babies and risk of long-term complications [99–106]. Several attempts have been made to sub-classify PE, according to severity, gestational age, initiating events and pathophysiological origin; furthermore, PE may be included in a continuum of diseases, from pregnancy-induced hypertension to HELLP syndrome (named for its three features: haemolysis, elevated liver enzymes, and low platelet levels) [107–112].

The classic definition of PE states that it is a reversible condition characterized by the association of hypertension and proteinuria (above 300 mg/day), occurring after the 20th week of pregnancy in previously normotensive, non proteinuric pregnant women [101]. Proteinuria and hypertension should disappear within 1–3 months after delivery. Some authors, however, recently suggested following PE patients for at least 6 months after delivery, to “change public (and clinician) thinking that pregnancy lasts, instead of 9 months, at least 15 months”. This idea is a great way of getting us all to consider the importance of post-partum care particularly for women with PE. In this way we can detect ongoing hypertension or renal issues [102]. The relationship with kidney diseases has been underlined by several authors, and is crucial for the differential diagnosis of PE [113–116].

A paradigm shift occurred when the American College of Obstetricians and Gynaecologists (ACOG) guidelines stated that PE may be diagnosed in the absence of proteinuria, basing diagnosis on new-onset hypertension accompanied by at least one of the following: serum creatinine increase, low platelet count or high liver enzymes, pulmonary edema or central nervous symptoms, once more...
underlining the central importance of kidney impairment in this context [117]. Independently from the definition, there are at least three conditions in which the differential diagnosis between PE and CKD is almost impossible: when no data before 20 gestational weeks is available; when CKD flares in pregnancy; when kidney disease develops in pregnancy [116, 118]. According to the widespread pathophysiological view, a placentation defect is at the basis of PE; thus, utero-placental flow analysis may help distinguish PE (impaired flows, and stunted growth) from CKD (normal blood flows and growth) [118–122]. Several clinical and biochemical biomarkers of PE have been suggested and could support the differential diagnosis between PE and CKD [123–131]. The ratio between sFlt-1, a receptor for both vascular endothelial growth factor (VEGF), and PIGF is considered as one of the most promising predictors of PE that may support the differential diagnosis between PE and CKD which, at least in the early stages, is characterized by a normal placentation [116, 118, 132–139].

Kidney biopsy is not recommended in pregnancy, according to a systematic review that highlights risks of severe bleeding complications. However, in early pregnancy, the pros and cons of diagnosis versus empiric therapy should be individually assessed, in particular in cases with progressive kidney function impairment. In late pregnancy, the advantages of an invasive manoeuver versus pre-term delivery should be considered [140]. A kidney biopsy should be performed in patients with persisting proteinuria [3–6 months after delivery (with the timing depending also on other renal parameters) without an established diagnosis of kidney disease. These patients are unfortunately often lost to follow-up, thus limiting the potential advantages of pregnancy as a first occasion for the diagnosis of potentially reversible CKD [32].

The Study Group therefore supports the need for systematic assessment of kidney function following PE, as well as in future pregnancies after PE or HELLP syndrome. While acknowledging the interest in serum biomarkers for the differential diagnosis between PE and CKD, the Study

| Drug                        | Characteristics                                                                                     | FDA               |
|-----------------------------|------------------------------------------------------------------------------------------------------|-------------------|
| **Semi-synthetic penicillin** | Ampicillin and Amoxicillin are the first-choice antibiotics                                         | B                 |
| Clavulanic acid             | Bacterial beta-lactamase inhibitor, used in combination with Amoxicillin. The association with beta-lactamase inhibitors is indicated when therapy with only Penicillins and Cephalosporins is not effective |                   |
| 1st and 2nd generation Cephalosporins | In general, the data available on the use of Cephalosporins, in particular of first and second generation, during pregnancy, does not indicate an increase, over the expectation, of congenital abnormalities on exposed new-borns |                   |
| 3rd generation Cephalosporins | Indicated for acute pyelonephritis when parenteral administration is necessary. Cefepime and Ceftriaxone: animal studies do not show teratogenic effects. Ceftriaxone should be avoided during the days before delivery because of the possibility of kernicterus (it competes with bilirubin for the binding with albumin) | B                 |
| Carbapenems                 | Meropenem should be the first choice in cases of notable severity, according to sensitivity. Animal studies, in fact, showed adverse effects on the foetus with Imipenem-cilastatin | B                 |
| Aztreonam                   | Valid alternative in the case of allergy to beta-lactams when parenteral administration is necessary | B                 |
| Macrolides                  | Erythromycin represents a valid alternative in the case of allergy to beta-lactams. Clarithromycin and Azithromycin are a second choice but they could be used according to clinical conditions [502] | B                 |
| Phosphomycin                | Indicated for uncomplicated urinary tract-infections [297, 298, 303]                               | B                 |
| Nitrofurantoin              | Contraindicated in G6PDH-deficient women. Their use during the first trimester should be limited to those situations in which no alternative therapies are available. Contraindicated at the end of the pregnancy (38th–40th week) and during delivery because of the risk of haemolytic anaemia in the new-born [26, 305] | B                 |

To be avoided

| Drug                        | Characteristics                                                                                     | FDA               |
|-----------------------------|------------------------------------------------------------------------------------------------------|-------------------|
| Aminoglycosides             | They have been associated with ototoxicity. Their use must be avoided                               | D                 |
| Fluoroquinolones            | Preclinical animal studies demonstrated abnormalities in the development of cartilages. Ciprofloxacin is not a first-choice drug during pregnancy; its administration should be limited to those cases in which the benefits are greater than the risk connected to the therapy [307] | C, D             |
| Tetracycline                | Their use must be avoided                                                                           | D                 |
| Sulphonamides               | Trimethoprim sulfamethoxazole must be avoided during the first trimester (it is a folic acid—antagonist) and at the end of the pregnancy for the risk of kernicterus | D                 |

FDA Classification [340]: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy
Table 4  Other drugs for pregnant CKD women

| Drug               | Characteristics                                                                 | FDA        |
|--------------------|---------------------------------------------------------------------------------|------------|
| **Usually considered as safe, when needed**                                    |                                                      |            |
| Acetylsalicylate    | Low doses during pregnancy needed for the treatment of diverse medical conditions have not been shown to cause foetal harm; may be protective against pre-eclampsia, favoring placentation (see text); discontinuation before delivery is recommended [161–163, 223, 224] | NC        |
| LMWH               | Low molecular-weight heparin (LMWH) does not cross the placenta and is safe for the foetus, although bleeding at the utero-placental junction cannot be ruled out. Individualized doses of LMWH are well tolerated and safe for prophylaxis and treatment of thromboembolic complications during pregnancy, and post-partum [355]. Twice-daily heparin should be discontinued prior to induction of labour or planned cesarean delivery and can be resumed after delivery [355, 356] | C         |
| ESAs               | In vitro studies suggest that recombinant erythropoietin does not cross the human placenta; higher doses may be needed in dialysis patients [357, 358] | C         |
| Allopurinol        | Adverse events were observed in animal studies. Allopurinol crosses the placenta [359]. An increased risk of malformations events has not been observed in humans (limited data) [360] | C         |
| Vitamin D          | The role for vitamin D supplementation in pregnancy is controversial, but there is no evidence of a reduction in adverse pregnancy outcomes (e.g., preeclampsia, stillbirth, neonatal death) [361] or improvement in bone mineral content in children in studies in which supplementation was given independently from blood levels [362]. Cholecalciferol (vitamin D3) crosses the placenta but the transfer to the foetus from the mother is low. Maternal supplementation has not been shown to affect pregnancy outcomes [363]. Ergocalciferol Adverse events were observed in animal studies. The ergocalciferol (vitamin D3) metabolite, 25(OH) D, crosses the placenta; maternal serum concentrations correlate with foetal concentrations at birth. Calcitriol Teratogenic effects have been observed in animal studies. Adverse effects on foetal development were not observed in women (N = 9) with pseudovitamin D-dependent rickets. Paricalcitol Adverse events were observed in some animal reproduction studies | C         |
| Vitamin D deficiency in a pregnant woman may lead to deficiency in the neonate [364, 365]. Serum 25(OH) D concentrations should be measured in pregnant women at increased risk of deficiency [366]. Current guidelines recommend an intake of 1000–2000 units/day until more safety data is available [366, 367]. Vitamin D and calcium levels should be monitored and kept in the lower normal range |            |

FDA Classification [340]: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy; NC, not classified

Group underlines that it is based on the results of few studies, mostly from the same groups, and envisages the organization of large multicentre studies on this issue.

Specific issues: hypertension as a complication of CKD and pregnancy

1. Arterial hypertension is a common complication of pregnancy in CKD, and should be early identified and treated (strong recommendation, indirect evidence from large observational studies).
2. “Overtreatment” should be avoided, due to the risk of reducing utero-placental flows, and inducing intrauterine growth restriction (strong recommendation, evidence from large observational studies).
3. Treatment should follow a stepwise approach, starting from the drugs with less contraindications in pregnancy (strong recommendation, based upon systematic reviews and guidelines).
4. When used for the antiproteinuric and nephron-protective effects, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) should be discontinued at the first assessment of a positive pregnancy test (strong recommendation for discontinuation, contrasting evidence for the timing).

Target blood pressure values are periodically reviewed in the hypertensive disorders of pregnancy, a setting in which a shared recommendation is to avoid overcorrection of hypertension, for the risk of affecting foetal growth [141–148]. Conversely, blood pressure targets in hypertensive CKD pregnancies are less established. It is presumably wise to avoid overcorrection, but it should also be remembered that hyperfiltration and proteinuria, that are widely described in hypertensive CKD patients, may have a detrimental effect on the kidney function [21].

Considering the recent Control of Hypertension In Pregnancy Study (CHIPS) trial, that revealed a substantial equivalence between “thigh and standard” blood pressure control in pregnancy, our group suggests implementing a strict blood pressure control (‘ideal’ target <130/80 mmHg, acceptable <140/90 mmHg), under careful clinical surveillance, at least in patients with good compliance that control blood pressure at home [149–152].

The main list of anti-hypertensive drugs is reported in Table 1. None is considered as fully safe. The issue of
The teratogenicity of ACEi and ARBs is still a matter of debate. The Study Group strongly supports early discontinuation of ACEi and ARBs at the first positive pregnancy test (4th–6th gestational week) in proteinuric CKD patients, to maximize the benefits of control of proteinuria, at least in compliant patients [153–158].

**Specific issues: proteinuria and low-protein diets**

1. Low-dose acetylsalicylate is indicated in proteinuric patients (as well as in patients with advanced CKD, SLE and immunoglobulin A nephropathy [IgAN]) (strong recommendation, different levels of evidence in the various diseases).

2. Albumin infusion is not indicated in nephrotic syndrome in pregnancy, since it may increase hyperfiltration and result in a further protein loss (medium recommendation, scattered evidence).

3. A moderate protein restriction may be of help in counterbalancing the hyperfiltration of pregnancy and may be safely employed in proteinuric patients and in patients with advanced CKD (medium recommendation, evidence from one group only).

The use of low-dose acetylsalicylate for the prevention of PE is suggested by a large body of evidence, in the cases at risk for PE, a category encompassing CKD patients (Table 4) [159, 160]. The timing is controversial. Most guidelines suggest starting therapy after the first trimester, because of the risk of haemorrhage in the case of early foetal loss. From a pathophysiological point of view, however, the effects on placentation should be maximal when aspirin is started early; therefore other authors suggest that an earlier start may be effective in preventing severe and early PE [161–163].

In the absence of clear evidence upon the best timing, the Study Group suggests to identify in each setting a shared policy between Obstetricians and Nephrologists,
taking also into account that our patients are more closely followed than the general population, thus potentially minimizing the risks of unexpected haemorrhage.

No study clearly identifies any benefit of albumin infusion in CKD and in PE, even if this empirical therapy is still diffused, with the aim of increasing albumin levels and reducing the risk of placental hypoperfusion. Therefore, the Study Group does not support the systematic use of albumin infusion in pregnant patients with nephrotic syndrome or PE, considering the potential risk of adverse reactions, and the risk of paradoxically increasing proteinuria by enhancing hyperfiltration [164–167].

In the absence of specific anti-proteinuric therapy in pregnancy, two non-randomised Italian reports suggest that a moderate protein restriction (0.6–0.8 g/kg/day), with a vegan-vegetarian diet supplemented with aminoacids and ketoacids, is feasible and safe in pregnant patients with CKD. Interestingly, the prevalence of small for gestational age babies was lower in on-diet patients as compared to patients on an unrestricted diet [168, 169]. The data obtained in a relatively small group of patients are in line with reports on the advantages of vegetal proteins in reducing kidney disease progression in non-pregnant humans, with a systematic review on vegan-vegetarian diets in pregnancy, and with the position of the American Dietary Association, provided that B12, iron and vitamin D are controlled and supplied upon need [170–178].

The Study Group suggests considering the diet option, at least in cases in which hyperfiltration (absolute or relative to the remnant nephrons) is supposed to play an important role, and strongly suggests organising multicentre studies on this issue.

Specific diseases: glomerulonephritis (primary)

1. The appearance of proteinuria during the third trimester of pregnancy calls for a differential diagnosis between glomerular disease and PE (strong recommendation, scattered evidence).
2. During pregnancy, glomerulonephritis may appear for the first time or be a relapse or worsening of a previously identified disease: the differential diagnosis is important for management (strong recommendation, evidence from large studies).
3. Proteinuria and nephrotic syndrome in pregnancy may suggest membranous glomerulonephropathy (MGN), minimal change nephropathy (MCN), or focal segmental glomerulosclerosis (FSGS) (strong recommendation, evidence from observational studies).
4. In patients with IgAN, the most common glomerulonephritis in the Mediterranean countries, pregnancy is not associated with a faster disease progression. Risk of disease progression after delivery is higher with GFR <70 ml/min/1.73 m², poorly controlled hypertension, and proteinuria (strong recommendation, evidence from observational studies).
5. Immunosuppressive therapy for primary glomerulonephritis needs to be re-evaluated in patients who wish to start pregnancy.

Many young women discover haematuria and proteinuria on the occasion of their first urinalysis during pregnancy and these urinary changes are often considered as pregnancy-related missing a diagnosis of underlying glomerular disease.

Microscopic haematuria is very common during pregnancy, detected in about 20 % of women, and disappears in 75 % after delivery [179]. Postpartum follow-up is recommended in women with persistent haematuria and presumed underlying glomerulonephritis, after excluding the presence of infection [180].

The development of proteinuria during pregnancy is often associated with PE. However, as previously discussed, isolated proteinuria or proteinuria with haematuria may reflect the presence of a renal disease. The most common forms of primary glomerulonephritis, in child-bearing age, are IgAN, FSGS, MCN, MGN, and
membrano-proliferative glomerulonephritis (MPGN); all may present with proteinuria and/or haematuria, occasionally with a rapidly progressive course.

The indication for renal biopsy is limited by the increase in bleeding risk; however, renal biopsy may be considered, in particular in early pregnancy, in the presence of rapidly progressive kidney function impairment or severe nephrotic syndrome [140].

IgA nephropathy

IgAN is the most prevalent primary glomerulonephritis worldwide, most often diagnosed in childbearing age. Proteinuria and/or hypertension in pregnancy are reported in up to 55% of cases, prematurity in 30% [181]. Several reports, including an Italian multicentre study on more than 200 pregnancies, suggest that pregnancy does not increase the progression of IgAN, at least in the earlier CKD stages. Favourable prognostic factors are normal blood pressure and GFR equal to or above 70 ml/min before conception [60, 181–186]. Proteinuria at conception was associated with renal function impairment after delivery, stressing the role for its reduction before pregnancy, thus supporting discontinuation of ACEi and ARBs at the first positive pregnancy test (see previous paragraph). In the case of rapid progression, the differential diagnosis may consider both severe PE and a superimposed kidney disease (such as haemolytic uremic syndrome) [187].

Other forms of primary glomerulonephritis

The incidence of primary nephrotic syndrome is approximately 3–5 cases per 100,000 inhabitants per year in children and adults. Albeit rare, all the main causes of primary nephrotic syndrome may present in pregnancy.
Some authors presently classify MCN and FSGS as ‘podocytopathies’ due to the characteristic podocyte damage or dysfunction [188]. Interestingly, podocyte impairment has been described in PE [126]. This may at least partly account for the reported, albeit debated, development of FSGS after PE [188–190]. FSGS associated with PE is characterized by an increase in glomerular size, as is observed in other forms of secondary FSGS such as obesity, in which hyperfiltration plays a central role [191].

While steroids are the first choice therapy in primary FSGS, prolonged treatment at high doses may have a detrimental effect on foetal growth [192]. Since the placental enzyme 11b-hydroxysteroid dehydrogenase 2 (11b-HSD2) protects the foetus reducing the transplacental passage of prednisolone, this drug may be preferred to betamethasone or dexamethasone [193, 194]. In the case of steroid resistance, calcineurin inhibitors may be added (Table 2).

Idiopathic membranous nephropathy (MN) often presents with a nephrotic syndrome; since, in over 70 % of patients with primary disease, autoantibodies against phospholipase A2 receptor 1 (PLA2R) are detectable by commercial kits, diagnosis may be performed without a kidney biopsy, which may, nevertheless, be required after pregnancy for staging [195]. A second target, thrombospondin type-1 domain-containing 7A (THSD7A) has been identified in a cohort of PLA2R-negative patients with MN, but is not yet clinically available [196]. In a study published in 1987, encompassing 33 pregnancies in 24 patients with MN, an increased foetal loss was observed, together with a risk of worsening of renal function [197]. This grim prognosis was not confirmed in a more recent cohort of nine MN patients with 51 pregnancies [198]. While steroids and calcineurin inhibitors are the milestones of treatment in pregnancy, addition of aspirin or low molecular-weight heparin should be considered, according to the clinical conditions.

Few studies and isolated case reports regard pregnancy in patients with primary MPGN, a multifaceted disease presently undergoing reclassification [199]. In a relatively old study on 123 pregnancies in 86 patients with biopsy-proven various glomerular diseases, a higher incidence of complications in MPGN patients versus MGN was observed [200]. However, the outcome was favourable in recent reports, including a case in which the nephrological decision to start steroid therapy instead of pregnancy termination, allowed to safely reach the end of gestation [201–203].

In conclusion, the Study Group calls for attention to the differential diagnosis of glomerulonephritis in pregnancy, and underlines the importance of pregnancy as the first occasion for diagnosis in apparently healthy women. The limits of the current evidence and the need for further studies targeted to the different nephropathies has to be further underlined.

Specific diseases: lupus nephritis as a prototype of systemic immunologic diseases

1. Before pregnancy, women with SLE should be accurately informed about the risks of pregnancies during active disease (strong recommendation, indirect evidence).
2. Severe pulmonary hypertension, severe restrictive lung disease, severe heart failure represent absolute contraindications to pregnancy (strong recommendation, scattered evidence).
3. Severe kidney function impairment (serum creatinine [sCr] >2.5 mg/dl, CKD stage 3–5) represents a relative contraindication to pregnancy (medium recommendation, scattered evidence).
4. Patients should be in remission for at least 6 months to reduce the risks of SLE flares in pregnancy (strong recommendation, scattered evidence).
5. Cyclophosphamide, mycophenolate and leflunomide have potential teratogenicity, and patients should be switched early to non teratogenic drugs (strong recommendation, scattered evidence).
6. Pregnant SLE women should be followed by a multidisciplinary team, in a tertiary care hospital (strong recommendation, indirect evidence).
7. Changes in immunosuppressive treatment in pregnancy should be limited to SLE flares; choice of treatment should be individualised (strong recommendation, indirect evidence).
8. Prednisone is considered safe. Intravenous immunoglobulin therapy is an effective and safe treatment for SLE pregnant patients with recurrent spontaneous abortions, especially if associated with antiphospholipid antibodies (strong recommendation, evidence from large series).
9. Low molecular-weight heparin with or without low-dose aspirin should be given to patients with SLE and antiphospholipid antibodies at high titres or triple positivity (strong recommendation, evidence from large series and RCTs).
10. An increase in glucocorticoid doses at time of delivery to prevent postpartum flares is a matter of debate (limited evidence).
11. Follow-up should be intensified postpartum since SLE flares may be more frequent in the first 6–12 months. Follow-up after PE should consider long-term cardiovascular complications (strong recommendation, evidence from large series).
12. Breastfeeding is allowed if prednisone does not exceed 20 mg/day. Azathioprine and cyclosporine are found in breast milk and lactation is not recommended (strong recommendation, evidence from large series).

SLE is a chronic autoimmune disease, primarily affecting young females with no influence on fertility. Pregnancy in women with SLE, and in those with lupus nephritis in particular, remains a high-risk situation for maternal and foetal complications [204–207]. The paucity of prospective studies on the subject makes evidence-based recommendations difficult; however, a number of retrospective cohort studies suggest that women with stable and prolonged remission of SLE, normal renal function, normal blood pressure and negative antiphospholipid antibodies have a high probability to have positive foetal and maternal outcomes [69, 204–212].

Since pregnancy-related risks are exceedingly high in SLE flares, effective contraceptive counselling is of paramount importance. Two large RCTs demonstrated the safety of oral contraceptives in SLE patients with inactive or mild active disease [213, 214]. However, patients with severe active disease or with antiphospholipid antibodies should not be treated with these drugs.

An extensive clinical, biochemical and immunological evaluation, in particular regarding the extractable nuclear antigen (ENA) profile and presence of antiphospholipid antibodies is necessary before pregnancy, together with a careful re-evaluation of the ongoing treatments [207, 209–211].

Cyclophosphamide should be withdrawn at least 3 months before pregnancy and mycophenolate shifted to azathioprine, as the European Medicine Agency (EMA) recommended in its 23/10/2015 warning. The shift from mycophenolate to azathioprine should be done at least 6 weeks before pregnancy in order to minimize the risk of SLE flares due to this change of therapy [215, 216]. Patients should start the pregnancy with the lowest possible dosage of the allowed drugs. Small birth weight and prematurity are associated with high-dose glucocorticoids, azathioprine and calcineurin inhibitors. Hydroxychloroquine reduces the rate of prematurity, intrauterine growth restriction and the risk of recurrent anti-SSA/Ro-antibodies associated cardiac manifestations in SLE pregnancy, and for these reasons should not be discontinued before pregnancy [217–219]. High-dose immunoglobulins are reported as safe and effective in SLE flares. Intravenous immunoglobulin therapy is an effective and safe treatment for SLE pregnant patients with recurrent spontaneous abortions, especially if associated with antiphospholipid antibodies [220–222].

Whether preeclampsia can be prevented by low dose aspirin is still a matter of debate, but current evidence supports its use in high risk populations [223, 224]. Low molecular-weight heparin with or without low-dose aspirin should be added to patients with SLE and antiphospholipid antibodies at high titres or triple positivity [225, 226].

In pregnancy, a strict multidisciplinary follow-up is indicated (Figs. 1, 2, 3, 4).

Maternal complications are relatively common: reactivation of lupus nephritis during pregnancy is reported to range between 15 to 30 % in studies published in the last two decades. Severe flares with impairment of renal function are infrequent, accounting for from none to 12 % of all cases [204–212]. The risk of PE is 3–5 times higher in SLE patients than in healthy women [211–227]. Substantial epidemiological data reveal that a history of PE increases the long-term cardiovascular risk by two to four times [228]. A recent meta-analysis on 1000 pregnancies in patients with lupus nephritis shows that arterial hypertension developed in 16.3 % of pregnancies [69]. Pregnancy-related hypertension predisposes to chronic hypertension, premature heart attacks, strokes, and renal complications [228].

Previous lupus nephritis and active lupus at conception are the most important predictors of all maternal complications [212–229]. The presence of antiphospholipid antibodies at high titres predisposes to arterial hypertension, PE, and to thrombotic microangiopathy during pregnancy. As already mentioned, renal function impairment and arterial hypertension at conception are predictors of poor maternal outcome whatever the underlying renal disease [230].

Foetal loss includes spontaneous abortion, stillbirth and neonatal death, and, based on a systematic review of 37
studies of lupus nephritis patients, they are estimated to occur, respectively, in around 16, 3.6, and 2.5 % of pregnancies [69]. Furthermore, based on a recent literature review, the rate of foetal loss in SLE pregnancies significantly decreased from a mean of 43 % in 1960–1965 to 17 % in 2000–2003 but continued to be higher than in the general population [231].

With the progressive reduction of foetal losses, the percentage of pregnancies that ends in premature birth has progressively increased, probably as a result of the immunological and vascular abnormalities associated with SLE. In lupus nephritis, approximately one-third of children are delivered preterm [205–210].

Neonatal lupus and congenital heart block are very rare complications, reported in less than 2 % of pregnancies, and are associated with positive SSA or SSB antibodies [232].

Several predictors of foetal outcome have been identified: high-activity of SLE in the first and second trimesters led to a threefold increase in pregnancy loss [233]. Active lupus nephritis at conception, and hypertension emerged as predictive factors for adverse foetal outcome in our as well as other authors’ experience [206, 227, 234].

As already mentioned, the presence of GFR less than 40 ml/min/1.73 m² and of proteinuria greater than 1 g/d before conception are strong predictors of poor foetal outcomes whatever the underlying renal disease [52–56]. A relatively old review of 10 studies of 554 women with SLE found that foetal loss ranged from 39 to 59 % in patients with antiphospholipid antibodies versus 18 % in those with negative antiphospholipid antibodies [235].

Overall, as underlined above, history of nephritis, active nephritis or active SLE at conception are the strongest predictors of adverse foetal and maternal outcome [236, 237]. For these reasons, a prerequisite for the success of pregnancy in patients with lupus nephritis is the planning of the pregnancy during periods of disease quiescence.

The study group therefore recommends to pay particular attention to pre-pregnancy counselling and to a strict multidisciplinary follow-up, in specialised Centres, in pregnancy in patients with SLE nephropathy.

Specific diseases: vasculitides

1. Pregnancies in women affected by vasculitides are rare. The presence of active disease or of disease diagnosed in pregnancy is associated with a higher risk of adverse pregnancy-related outcomes (strong recommendation, scattered evidence).

2. A strict, multidisciplinary follow-up should be planned in tertiary care Centres to identify the best, personalised therapeutic strategies and the best balance between pregnancy termination, risks of early delivery and maternal risks (strong recommendation, indirect evidence).

Pregnancies are very rare in women affected by systemic vasculitides. The main reason is that, except for Takayasu disease, the peak age is typically over 40 years; the multi-organ involvement usually discourages the few patients in childbearing age from planning a pregnancy. Furthermore, the most frequently used immunosuppressive drugs, above all cyclophosphamide, contraindicate pregnancy and may induce premature menopause and sterility. However, with earlier diagnosis and new treatments, pregnancies in these patients will probably increase.

Because of the rarity of pregnancy, data on clinical management and maternal and foetal outcomes are based on few series, from experienced referral centres, and on case reports. Within these limits, some important points for risk assessment may be identified [238–245].

With regards to disease activity at conception, three situations are possible: pregnancies electively planned in remission and conducted under a strict multidisciplinary surveillance; unplanned pregnancies in patients on treatment; de novo or relapsing systemic vasculitis during pregnancy.

Pregnancy in patients affected by vasculitis in remission, undergoing planned multidisciplinary follow-up are reported to have good maternal and foetal outcomes, provided treatment is strictly monitored, to avoid relapses. Most published cases fall into this category (usually milder and often localized disease). However, some authors outline specific risks, mainly in the last weeks of pregnancy, including cardiac failure, asthma or decompensating subglottic stenosis.

The materno-foetal risks are higher in patients who get pregnant in a phase of active disease, who relapse or who develop de novo vasculitis during pregnancy. In this setting, ominous maternal and foetal complications have been reported. Among the life-threatening complications, pulmonary haemorrhage, rapidly progressive glomerulonephritis, polyneuritis and myocarditis have been described.

In the setting of kidney involvement and hypertension, the differential diagnosis between vasculitis and PE may be difficult; whatever the cause, hypertension and renal impairment may persist after delivery.

Therapeutic strategies need to be individualised. Patients should be aggressively treated in the case of flares or of active disease. Pregnancy termination or induction of delivery should be considered in these cases. Low-dose acetylsalicylic acid may be indicated for PE prevention. High-dose intravenous (iv) steroids, plasma-exchange, high-dose immunoglobulin, and azathioprine may allow
continuation of pregnancy in an attempt to find a balance between maternal and foetal risks [238–245]. For further therapeutic issues, please refer to Tables 1, 2, 3 and 4.

Acknowledging the scarce experience on this issue, the Study Group strongly recommends that patients with systemic vasculitis should be referred to tertiary care Centres to undergo a strict, personalised, multidisciplinary follow-up.

Specific diseases: diabetic nephropathy

1. Diabetic nephropathy is associated with a higher risk of perinatal death as compared with other primary causes of CKD (evidence from several studies on diabetes, no specific comparison with other causes of CKD).
2. There may be a higher incidence of malformations in diabetic nephropathy as compared to diabetes per se, in which an in increase in malformation has been reported (important recommendation, one large study only reporting higher risk of malformations in diabetic nephropathy).
3. Proteinuria may steeply rise in pregnant women with diabetic nephropathy, making the differential diagnosis with PE very difficult (strong recommendation, scattered data).
4. Prenatal counselling is fundamental to reduce the risks linked to poor glycaemic control and to optimize multidisciplinary follow-up (malformations, prematurity, large for gestational age babies).

The evidence regarding diabetic nephropathy in pregnancy is limited. In a recent systematic review, out of thirty-four papers retrieved, only two reported on more than 100 patients, while most studies described less than 50 cases [28]. When diabetic nephropathy is broadly defined as presence of any sign of renal disease including microalbuminuria, its prevalence ranges from 5 to over 25 % in type 1 diabetic pregnant women.

During pregnancy, diabetes per se has been associated to a variety of complications, including malformations, foetal growth impairment, stillbirth, early mortality and preterm delivery while the incidence of PE has been reported as significantly increased, even if this is always within the limits of the non-univocal definition of this term [28–30, 246–250].

Maternal outcomes are widely scattered and probably reflect several factors: the lack of univocal definitions of diabetic nephropathy, CDK and PE, increasing maternal age over time, different study aims, patients selection and setting of several studies, small sample size and single-centre and care settings.

While the high risk of prematurity, small for gestational age babies, or intrauterine growth restriction is shared also by other kidney disorders and increases along with the progression of kidney disease, stillbirth or foetal death are shared only by SLE, sharing with diabetes the important microvascular damage [62, 242]. The risk is present also in diabetic patients without overt nephropathy, but appears to be increased in the setting of diabetic nephropathy [28–30]. Interestingly, even if in the last period, the risks of stillbirth and foetal death are reduced with respect to the ‘80s (from over 10 to about 5 %), the reduction is much lesser than that observed in the case, for example, of mothers on dialysis, which has decreased by 25 % each decade since the ‘80s, albeit starting from a much higher level [28–30].

Only one recent paper specifically reported on malformations in diabetic nephropathy, described as increased compared to diabetic patients without nephropathy [91]. While these data, obtained in a large cohort, are waiting for further confirmation, a note of caution should probably be made at counselling.

Acknowledging the need for further research in this field, the Study Group suggests a strict multidisciplinary follow-up, paying attention to the concomitant factors, such as hypertension and diabetes, that may further increase pregnancy related complications, and suggests strict follow-up also after delivery, in particular in patients who developed severe proteinuria and hypertension (whether or not labelled as PE) during pregnancy [251–258].

Specific diseases: autosomal-dominant polycystic kidney disease

1. ADPKD patients may have a higher risk of pyelonephritis in pregnancy and should be strictly controlled for positive urinary cultures (moderate suggestion, scattered evidence).
2. ADPKD patients may be at higher risk for PE, also when pregnancy starts with normal blood pressure and without proteinuria (moderate suggestion, scattered evidence).
3. The Study Group does not support a policy of systematic caesarean delivery in ADPKD patients (moderate suggestion, scattered evidence).
4. While acknowledging the interest in pre-implantation genetic selection, as a potential tool in autosomal recessive PKD, there is no experience on ADPKD, and the problems linked to assisted fertilization procedures have to be carefully weighed up (moderate suggestion, scant evidence).

The evidence on ADPKD in pregnancy is limited, and the largest recently published series encompasses 54 patients
only [259]. In keeping with older observations, the current evidence suggests that hypertensive disorders of pregnancy, including PE, are more frequent in ADPKD patients. Preterm delivery and UTIs were also found to be increased, but the relationship between them is not completely clarified [259–262].

The old tenet that women with ADPKD should deliver by caesarean section because of the risk of intracystic bleeding, due to the increased abdominal pressure at parturition, is not supported by current evidence, also considering the risks of a surgical intervention and of urinary catheter. However, some cases have also recently been reported, and the opinion of the Study Group is that the risk of intracystic bleeding should be considered; therefore, we suggest ultrasound monitoring in particular of the largest cysts, also in non-symptomatic patients, at least in the proximity of and immediately after delivery [262–264].

The Group does not presently support the choice of implantation selection procedures, given their non-negligible rate of complications; such an approach has been recently discussed as for autosomal-recessive polycystic kidney disease, where, in spite of the higher severity of the disease, there is no clear evidence for an increased risk of intracystic bleeding, and it is likewise controversial [265, 266].

Specific diseases: chronic pyelonephritis, kidney scars and diseases at risk for upper urinary tract infections in pregnancy (including kidney stones)

1. Asymptomatic bacteriuria, acute cystitis and acute pyelonephritis have been associated with an increased risk of abortion, preterm delivery, low birth weight and perinatal mortality. Gestational hypertension and PE are also increased (relative risk [RR] up to 5) (strong suggestion, from large observational studies).

2. Since untreated, asymptomatic bacteriuria persists in 60–85 % of cases and progresses to acute cystitis or pyelonephritis in up to 40 % of patients, all cases should be treated (strong suggestion, from large observational studies and RCTs).

3. Antibiotic therapy allows sterilization of urinary culture in 90 % of patients and reduces the incidence of acute pyelonephritis by 70–80 %, decreasing the incidence of low birth-weight and of preterm birth (strong suggestion, from large observational studies and RCTs).

4. The optimal treatment for asymptomatic bacteriuria, acute cystitis and acute pyelonephritis is not fully established. Empiric treatment should be tailored to the specific situation and take into account the local resistance patterns (strong suggestion, from large observational studies and RCTs).

Chronic pyelonephritis is now recognized as an umbrella term encompassing many chronic inflammatory conditions even in the absence of a clear history of renal infections [267]. Whatever the cause, kidney scars, identified by imaging techniques, define this condition [268–271]. Risk of bacteriuria is significantly higher in women with a history of UTI in childhood and adolescence, whether or not with kidney scars [271]. The incidence of asymptomatic bacteriuria is estimated to be 2–7 % of all pregnancies (more common in diabetic women: 8–14 %); acute pyelonephritis occurs in 1–2 % of low-risk pregnancies [272–276].

Pregnancy predisposes to UTI for several reasons: the physiological hydroureter of pregnancy, consequent to progestosterone-induced hypotonia and decreased peristaltic activity and to the compression of the gravid uterus; pregnancy-induced glycosuria and aminoaciduria may facilitate bacterial colonization, immune-system changes, including reduced response to nitric oxide (NO) and Toll-like receptor 4 (TLR4) [277, 278].

In planning the clinical surveillance, several risk factors should be considered: history of UTI, diabetes, low socioeconomic status, older age, sickle-cell anaemia, urological abnormalities, sexual activity, and multiparity [277–279].

Asymptomatic bacteriuria has been associated with an increased risk of abortion, preterm birth, low birth-weight and perinatal mortality, thus leading to the current practice of repeated urinalysis and urinary cultures in all pregnancies [280–284].

The relationship between asymptomatic bacteriuria, low birth-weight and preterm delivery is however still elusive. Pro-inflammatory cytokines may initiate labour, while microorganisms may produce arachidonic acid, phospholipase A2 and prostaglandins that enhance cervical softening, which stimulates uterine contractions and preterm labour [285]. If untreated, bacteriuria persists in 60–85 % of cases, progressing to cystitis or pyelonephritis in up to 40 % of patients, and increasing the risk of PE [273, 279].

Antibiotic therapy allows sterilization of urinary culture in 90 % of patients and reduces the risks of acute pyelonephritis, along with low birth-weight babies and preterm birth [274, 280, 286–299].

The therapeutic protocols are controversial: single-dose therapy and 3-day courses were used with success in some studies. The pros are better compliance, lesser exposure for the foetus, fewer side effects, lower costs; the con is the higher recurrence rate. On this basis, the Study Group supports standard 6–7 days antibiotic courses until further data are available [300–302]. Follow-up requires at least monthly urine culture and, in case of persistence, suppressive therapy should be considered. For the most commonly used drugs, refer to Table 3.
Acute cystitis is frequently asymptomatic; conversely, acute pyelonephritis usually presents with flank abdominal or pelvic pain, and high fever; severe complications, including septic shock, respiratory distress and acute renal failure are reported in 2–25% of cases [303–318]. Since Escherichia Coli is involved in about 80% of the cases and other Gram negative germs in most of the remaining, empirical treatment should be started early on the basis of the local resistance pattern and of the eventual maternal intolerances (Table 3) [319, 320]. Preeclampsia and preterm delivery are reported as increased after UTI in pregnancy, even in the absence of active infection at delivery [321].

**Kidney stones**

1. Kidney stones are rare in pregnancy, but they are associated with several negative pregnancy-associated outcomes, including PE and preterm delivery (strong suggestion, evidence from observational studies).

2. Within the limits of the scarce urethral view, ultrasound should be the first imaging modality, while magnetic resonance imaging (MRI) and computed tomography (CT) scans (II and III trimester) should be limited to selected cases (strong suggestion, scattered evidence).

3. While most of the stones are passed spontaneously, ureteroscopy is relatively safe in the case of need; small series suggest considering also the option of holmium laser (strong suggestion, large series for ureteroscopy, small for holmium laser).

Nephrolithiasis is rare in pregnancy (1:1500–3000), despite several predisposing factors, including urinary stasis, hypercalciuria and increased urinary pH, increased excretion of uric acid, sodium and oxalates, out of proportion with citrate and magnesium excretion [322]. Calcium and phosphate are the most frequent components of kidney stones in pregnancy (up to 75%) [322–324].

Renal colics are more frequent in the second and third trimester; gross hematuria may occur in about one-third of cases [325–332]. Ultrasounds allow limited visualization of ureteral stones; ureteral jet can discriminate between physiological hydrouretere and complete obstruction. Doppler study and resistivity index may help in the diagnosis while transvaginal ultrasounds can highlight stones into the distal ureter [322–327]. In selected cases MRI may be required [328].

In most cases, the dilation of the urinary tract favours stone emission and only symptomatic therapy, based on hydration and analgesia is needed. Ureteral stents, percutaneous nephrostomy or ureteroscopy may be employed in selected cases, as well as holmium laser lithotripsy, according to small patient series [325–331].

Renal stents have been associated with increase in proteinuria to be considered in the differential diagnosis with PE [332]. The association with nephrocalcinosis should be kept in mind for allowing diagnosis of underlying metabolic disorders [333].

In view of the above, considering also the possible association between renal colic, premature rupture of membranes, pregnancy losses and PE, the Study Group suggests a strict multidisciplinary follow-up and personalised therapy for all patients with recurrent UTI or kidney stones [334–337].

**Reflux nephropathy**

1. Patients with reflux nephropathy are at higher risk for urinary tract infections even after reflux correction.

2. Reflux nephropathy shows a complex hereditary pattern and children from affected mothers should be screened before and after birth for UT and/or urinary malformations.

The frequent correction of reflux nephropathy has decreased its importance in pregnancy, and most of the studies related to this condition are relatively old. While the surveillance for infectious complications should follow the strict recommendations already mentioned in the case of recurrent UTI, the disease shows a complex hereditary pattern, and children from affected mothers should be screened before and after birth for UTI and/or urinary malformations [338–340].

**Final comment**

CKD is increasingly encountered in pregnancy and patients with chronic diseases, including CKD, are increasingly looking for pregnancies. Due to the changes in therapies, and in attitudes towards patients’ self-determination as well as in the definitions of CKD and PE, the evidence on which counselling and follow-up are based is often scattered and fragmentary. This lack of “certitudes” should be kept in mind at counselling, and strongly supports shared choices in the context of multidisciplinary care. Clinical nephrologists need to be continuously updated in this emerging field, and the Study Group supports the establishment of educational programs and of multicentre research studies.

**Compliance with ethical standards**

Conflict of interest All authors have no conflict of interest.
Ethical approval  This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent  For this type of study informed consent is not required.

References

1. (1975) Pregnancy and renal disease. Lancet 2(7939):801–802
2. Duffy D, Reynolds P (2011) Babies born at the threshold of viability: attitudes of paediatric consultants and trainees in South East England. Acta Paediatr 100(1):42–46
3. Hale TM, Arul M, Veerappan A, Nguyen J, Velastegui Z, Shiffman R, Rajegowda B, Skupski D, Mercado R (2011) Predicting survival of periviable fetuses using NICHD fetal heart rate categories. J Perinat Med 39(1):47–50
4. Stephens BE, Tucker R, Vohr BR (2010) Special health care needs of infants born at the limits of viability. Pediatrics 125(6):1152–1158
5. Hou SH (1994) Pregnancy in women on haemodialysis and peritoneal dialysis. Baillieres Clin Obstet Gynaecol 8:481–500
6. Piccoli GB, Conijn A, Consiglio V et al (2010) Pregnancy in dialysis patients: is the evidence strong enough to lead us to change our counseling policy? Clin J Am Soc Nephrol 5:62–71
7. Hladunewich MA, Hou S, Ohtatoyo A et al (2014) Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States Cohort Comparison. J Am Soc Nephrol 25(5):1103–1109
8. Toma H, Tanabe K, Tokumoto T, Kobayashi C, Yagisawa T (1999) Pregnancy in women receiving renal dialysis or transplantation in Japan: a nationwide survey. Nephrol Dial Transplant 14:1511–1516
9. Luders C, Castro MC, Titan SM et al (2010) Obstetric outcome in pregnant women on long-term dialysis: a case series. Am J Kidney Dis 56:77–85
10. Jesudason S, Grace BS, McDonald SP (2014) Pregnancy outcomes according to dialysis commencing before or after conception in women with ESRD. Clin J Am Soc Nephrol 9:143–149
11. Piccoli GB, Cabiddu G, Daidone G et al (2014) Intensive dialysis in pregnancy and the overall population. Nephrol Dial Transplant 29(8):1578–1586
12. Piccoli GB, Postorino V, Cabiddu G et al (2015) ‘Kidney and Pregnancy Study Group’ of the ‘Italian Society of Nephrology’. Children of a lesser god or miracles? An emotional and behavioural profile of children born to mothers on dialysis in Italy: a multicentre nationwide study 2000–12. Nephrol Dial Transplant 30(7):1193–1202
13. Cabiddu G, Castellino S, Gernone G et al (2015) Kidney and Pregnancy Study Group of Italian Society of Nephrology. Best practices on pregnancy on dialysis: the Italian Study Group on Kidney and Pregnancy. J Nephrol 28(3):279–288
14. www.kidney.org. Accessed 20 Sept 2015
15. Winears CG, Glassock RJ (2009) Dissecting and refining the staging of chronic kidney disease. Kidney Int 75:1009–1014
16. Smyth A, Radovic M, Garovic VD (2013) Women, kidney disease, and pregnancy. Adv Chronic Kidney Dis 20:402–410
17. Davison JM, Lindheimer MD (2011) Pregnancy and chronic kidney disease. Semin Nephrol 31:86–99
18. Williams D, Davison J (2008) Chronic kidney disease in pregnancy. BMJ 33:211–215
19. Nevis IF, Reitsma A, Dominic A et al (2011) Pregnancy outcomes in women with chronic kidney disease: a systematic review. Clin J Am Soc Nephrol 6:2587–2598
20. Piccoli GB, Conijn A, Attini R et al (2011) Pregnancy in chronic kidney disease: need for a common language. J Nephrol 24:282–299
21. Zhang JJ, Ma XX, Hao L, Liu LJ, Lv JC, Zhang H (2015) A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD Outcomes in pregnancy. Clin J Am Soc Nephrol 10(11):1964–1978
22. Lateef A, Petri M (2013) Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol 27:435–447
23. Stanhope TJ, White WM, Moden KG et al (2012) Obstetric nephrology: lupus and lupus nephritis in pregnancy. Clin J Am Soc Nephrol 7:2089–2099
24. Vora N, Perrone R, Bianchi DW (2008) Reproductive issues for adults with autosomal dominant polycystic kidney disease. Am J Kidney Dis 5:307–518
25. Chapman AB, Johnson AM, Gabow PA (1994) Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 5(5):1178–1185
26. Schneeberger C, Geerlings SE, Middleton P, Crowther CA (2012) Interventions for preventing recurrent urinary tract infection during pregnancy. Cochrane Database Syst Rev 11:CD009279
27. Podymow T, August P, Akbari A (2010) Management of renal disease in pregnancy. Obstet Gynecol Clin N Am 37(2):195–210
28. Piccoli GB, Clari R, Ghiozzo S et al (2013) Type 1 diabetes, diabetic nephropathy, and pregnancy: a systematic review and meta-study. Rev Diabet Stud 10:6–26
29. Piccoli GB, Stanovolo E, Melluzzo C et al (2013) Severe diabetic nephropathy in type 1 diabetes and pregnancy—a case series. Rev Diabet Stud 10:68–78
30. Bramham K, Rajasingham D (2012) Pregnancy in diabetes and kidney disease. Ren Care 38(Suppl 1):78–89
31. Garovic VD (2000) Hypertension in pregnancy: diagnosis and treatment. Mayo Clin Proc 75(10):1071–1076
32. Piccoli GB, Fassio F, Attini R et al (2012) Pregnancy in CKD: whom should we follow and why? Nephrol Dial Transplant 27(Suppl 3):iii111–iii118
33. Morikawa M, Yamada T, Minakami H (2009) Outcome of pregnancy in patients with isolated proteinuria. Curr Opin Nephrol Hypertens 18:199–204
34. Smith MC, Moran P, Ward MK, Davison JM (2008) Assessment of glomerular filtration rate during pregnancy using the MDRD formula. BJOG 115:109–112
35. Krutzén E, Olofsson P, Bäck SE, Nilsson-Ehle P (1992) Kidney transplantation protective in chronic kidney disease-stage 1 pregnancies? A meta-study. Rev Diabet Stud 10:6–26
36. Ahmed SB, Bentley-Lewis R, Hollenberg NK et al (2009) A comparison of prediction equations for estimating glomerular filtration rate in pregnancy. Hypertens Pregnancy 28:243–255
37. Alper AB, Yi Y, Rahman M, Webber LS et al (2011) Performance of estimated glomerular filtration rate prediction equations in pre eclamptic patients. Am J Obstet Gynecol 216(6):491–495
38. Smith MC, Moran P, Ward MK, Davison JM (2008) Assessment of glomerular filtration rate during pregnancy using the MDRD formula. BJOG 115:109–112
39. Krutzén E, Olofsson P, Bäck SE, Nilsson-Ehle P (1992) Glomerular filtration rate in pregnancy: a study in normal subjects and in patients with hypertension, preeclampsia and diabetes. Scand J Clin Lab Invest 52:387–392
40. Ahmed SB, Bentley-Lewis R, Hollenberg NK et al (2009) A comparison of prediction equations for estimating glomerular filtration rate in pregnancy. Hypertens Pregnancy 28:243–255
41. Alper AB, Yi Y, Rahman M, Webber LS et al (2011) Performance of estimated glomerular filtration rate prediction equations in pre eclamptic patients. Am J Obstet Gynecol 216(6):491–495
42. Piccoli GB, Attini R, Vigotti FN et al (2015) Is renal hyperfiltration protective in chronic kidney disease-stage 1 pregnancies? A step forward unravelling the mystery of the effect of stage 1 chronic kidney disease on pregnancy outcomes. Nephrology (Carlton) 20(3):201–208
43. Gülmezoglu M, Villar J, Hofmeyr J, Duley L, Belizan JM (1998) Randomised trials in maternal and perinatal medicine:
development and validation of the fullPIERS model. Lancet 377(9761):219–227

124. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 330:565

125. Garovic VD, Wagner SJ, Turner ST et al (2007) Urinary podocyte excretion as a marker for preeclampsia. Am J Obstet Gynecol 196(4):320.e1–7

126. White WM, Garrett AT, Craici IM et al (2014) Persistent urinary podocyte loss following preeclampsia may reflect subclinical renal injury. PLoS One 9(3):e92693

127. Thangaratnam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS (2006) Tests in Prediction of Pre-eclampsia Severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 113(4):369–378

128. Dusse LM, Alpoim PN, Lwaleed BA et al (2013) Is there a link between endothelial dysfunction, coagulation activation and nitric oxide synthesis in preeclampsia? Clin Chin Acta 16(415):226–229

129. George EM, Granger JP (2011) Endothelin: key mediator of hypertension in preeclampsia. Am J Hypertens 24(9):964–969

130. Bilodeau JF (2014) Review: maternal and placental antoxidant response to preeclampsia—impact on vasoactive eicosanoids. Placenta 35(Suppl):S32–S38

131. Gennari-Moser C, Khankin EV, Escher G et al (2013) Vascular endothelial growth factor-A and aldosterone: relevance to normal pregnancy and preeclampsia. Hypertension 61(5):1111–1117

132. Rana S, Powe CE, Salahuddin S et al (2012) Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation 125(7):911–919

133. Moore Simas TA, Crawford SL, Solitiro MJ, Frost SC, Meyer BA, Maynard SE (2007) Angiogenic factors for the prediction of preeclampsia in high-risk women. Am J Obstet Gynecol 197(3):244.e1–8

134. Duhig KE, Chappell LC, Shennan AH (2014) How placental growth factor detection might improve diagnosis and management of preeclampsia. Expert Rev Mol Diagn 14(4):403–406

135. Verlohren S, Herraiz I, Laprairie O et al (2012) The sFlt-1/PlGF and sFlt-1/PlGF ratio: usefulness in diagnosis of preeclampsia. BJOG 119(7):1210–1218

136. Molvi SN, Mir S, Rana VS et al (2012) Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a heterogeneous maternal response impacts fetal growth. Am J Hypertens 23:1234–1240

137. Collins R, Yusuf S, Peto R (1985) Overview of randomised trials of diuretics in pregnancy. Br Med J 290:17–23

138. Firoz T, Magee LA, MacDonell K, Payne BA, Gordon R, Vidler M, von Dadelszen P (2014) Community Level Interventions for Pre-eclampsia (CLIP) Working Group. BJOG 121(10):1210–1218

139. Nabhan AF, Elsedawy MM (2011) Tight control of mild-moderate pre-existing or non-proteinuric gestational hypertension. Cochrane Database Syst Rev 7:CD006907

140. Magee LA, von Dadelszen P, Rey E et al (2015) Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 372(5):407–417

141. Magee LA, CHIPS Study Group et al, von Dadelszen P et al (2015) Control of hypertension in pregnancy study randomised controlled trial—are the results dependent on the choice of labetol or methyldopa? BJOG. doi: 10.1111/1471-0528.13568

142. Firoz T, Magee LA, MacDonell K, Payne BA, Gordon R, Vidler M, von Dadelszen P, Community Level Interventions for Pre-eclampsia (CLIP) Working Group (2014) Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review. BJOG 121(10):1210–1218 (discussion 1220)

143. Wise J (2015) Tight blood pressure control during pregnancy offers no clear benefits, study finds. BMJ 2(350):h549

144. Huyhn K (2015) Hypertension: tight control of hypertension is safe in pregnant women. Nat Rev Cardiol 12(4):196

145. Cooper WO, Hernandez-Diaz S, Arbogast PG et al (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 355(2):17–23

146. Lewis G, Maxwell AP (2014) Should women with diabetic nephropathy considering pregnancy continue ACE inhibitor or angiotensin II receptor blocker therapy until pregnancy is confirmed? Diabetologia 57(5):1082–1083

147. Koren G (2011) Hypertension: ACE inhibitor use in pregnancy—setting the record straight. Nat Rev Cardiol. 9(1):7–8. doi:10.1038/nrcardio.2011.179

148. Liu J, Truong M (2014) Should women with diabetic nephropathy considering pregnancy continue ACE inhibitor or angiotensin II receptor blocker therapy until pregnancy is confirmed? Diabetologia 57(5):1082–1083

149. Cooper WD, Hernandez-Diaz S, Arbogast PG et al (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 354:2443–2451

150. Li DK, Yang C, Andrade S, Tavares V, Ferber JR (2011) Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ 343:d5931

151. Vasilikis-Scaramozza C, Aschengrau A, Cabral HJ, Jick SS (2013) Antihypertensive drugs and the risk of congenital anomalies. Pharmacotherapy 33:476–482

152. Al-Balas M, Bozzo P, Einarson A (2009) Use of diuretics during pregnancy. Can Fam Physician 55(1):44–45

153. Henderson JT, Whitlock EP, O’Conner E, Senger CA, Thompson JM, Rowland MG (2014) Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Report No.: 14-05207-EP-1. US Preventive
238. Doria A, Bajocchi G, Tonon M, Salvarani C (2008) Pre-pregnancy counselling of patients with vasculitis. Rheumatology 47:iii13–iii15
239. Pagnoux C, Le Guern V, Goffinet F et al (2001) Pregnanacies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology 50:953–961
240. Tuin J, Sanders JSF, de Joode AAE, Guideline Development Group (2010) Management of women with pregestational diabetes. Endocrinol Obstet Gynecol 193(6):1923–1935
241. Flakoll P, Amundsen B, Storjohann S, et al (2011) Pregnancy outcome among patients with vasculitis. Arthritis Care Res (Hoboken) 64:539–545
242. Croft AP, Smith SW, Carr S et al (2015) Successful outcome of pregnancy in patients with anti-neutrophil cytoplasm antibody-associated small vessel vasculitis. Kidney Int 87:807–811
243. Sangle SR, Vounotrypidis P, Briley A et al (2015) Pregnancy outcomes in women with and without pre-existing microalbuminuria. Br Med J 299:366–367
244. Soh MC, Klamut M, Caban B, Wieczorek P, Tereszkwiecik J (1988) Superselective arterial embolization in the control of hemorrhage from ruptured cyst in polycystic kidney in pregnancy. Pol Przegl Radiol 52(2):110–111
245. Backe J, Kristen P, Arlt W, Steck T (1996) Postpartum rupture of a kidney cyst in familial polycystic kidney degeneration and HELLP syndrome. Z Geburtshilfe Neonatol 200(3):122–126
246. Niessen LR, Damm P, Mathiesen ER (2009) Improved pregnancy outcome in women diagnosed with ANCA-Associated Vasculitis: favorable outcome for mother and child. Arthritis Care Res 65(1370):1374
247. Nicolle LE (2012) Urinary tract infection in adults. In: Brenner and Rector's the kidney, 9th edn. Saunders. ISBN: 978-1-4160-6193-9, 36, pp 1356–1382
248. Banks N, Bryant J, Fischer R, Huizing M, Gahl WA, Gunay-Aygun M (2015) Pregnancy in autosomal recessive polycystic kidney disease. Arch Gynecol Obstet 291(3):705–708
249. Aygun M (2015) Pregnancy in autosomal recessive polycystic kidney disease. Reprod Biomed Online. 16(1):152–158
250. Chapman AB, Johnson AM, Gabow PA (1994) Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 5(11):1178–1185
251. Aygun M (2015) Pregnancy in autosomal recessive polycystic kidney disease. Reprod Biomed Online. 16(1):152–158
365. Wagner CL, Greer FR, The Section on Breastfeeding and Committee on Nutrition (2008) Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 122(5):1142–1152
366. ACOG Committee on Obstetric Practice (2011) ACOG Committee Opinion No. 495: vitamin D: screening and supplementation during pregnancy. Obstet Gynecol 118(1):197–198
367. Holick MF, Binkley NC, Bischoff-Ferrari HA et al. (2011) Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline (published correction appears in J Clin Endocrinol Metab 2011;96(12):3908). J Clin Endocrinol Metab. 2011;96(7):1911–1930
368. Piccoli GB, Cabiddu G, Attini R et al (2015) Pregnancy in chronic kidney disease: questions and answers in a changing panorama. Best Pract Res Clin Obstet Gynaecol 29(5):625–642
369. Chakravarty EF, Murray ER, Kelman A, Farmer P (2011) Pregnancy outcomes after maternal exposure to rituximab. Blood 117(5):1499–1506
370. Klink DT, van Elburg RM, Schreurs MW, van Well GT (2008) Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. Clin Dev Immunol. 2008:271363. doi:10.1155/2008/271363