Update on Pregnancy in Chronic Kidney Disease

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Abstract
The occurrence of pregnancy in patients with chronic kidney disease (CKD) has been considered a dangerous event both for the mother and for the fetus. However, increasing evidence shows that the stage of CKD is the leading factor that can predict possible acceleration in the declining of renal function and complications of pregnancy. This review summarizes recent data on pregnancy in patients with CKD, dialysis and kidney transplantation.

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Discovery of Renal Dysfunction during Pregnancy

Pregnancy is probably the major physiologic event that can induce profound changes in renal function. The glomerular filtration rate (GFR) as well as the local production of erythropoietin and vitamin D [1, 2] increase by more than 50%. The increase in GFR is due to an augmented renal blood flow, not to an increased intraglomerular pressure [3]. However, in the presence of chronic kidney disease (CKD), this physiological adaptation is reduced or absent [1]. Therefore, a woman with undiagnosed renal dysfunction might present the first symptoms and signs during pregnancy.

First, it is important to realize that the measurement of renal function in pregnant women is still not standardized. Given the increase in GFR, the concentration of serum creatinine usually falls to 0.4–0.6 mg/dl (35–55 μmol/l). This event does not occur in patients with renal dysfunction, where a level of serum creatinine around 1–1.2 mg/dl (90–110 μmol/l) could be considered physiologic [4]. On the contrary, these values should be seen as the first signs of renal dysfunction. In addition, the use of the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault formulas has never been validated in this population [5]. In a study on 209 women with preeclampsia [6], the Cockcroft-Gault formula overestimated the GFR by approximately 40 ml/min, whereas the MDRD formulas underestimated the GFR (by 19.68 ml/min for the full MDRD and by 12.6 ml/min for the modified MDRD). Therefore, the gold standard for GFR estimation in pregnancy is still considered to be the 24-hour urine collection for creatinine clearance [7].

Once renal dysfunction has been identified, the family doctor should refer the patient to the nephrologist, who would start a clinical and biochemical monitoring throughout the pregnancy. The frequency of the monitoring should increase with the progression of pregnancy, including the measurement of the mother's renal function, analysis of the urine, and blood pressure. Renal ultrasound should be performed. Methods for measuring proteinuria should be the urine protein-to-creatinine ratio or, in the presence of equivocal results, the 24-hour collection can be considered [8]. The monitoring of pro-

teinuria is very relevant to the diagnosis of preeclampsia and in patients with a history of proteinuric kidney disease such as glomerulonephritis.

Factors Influencing the Acceleration of CKD

Pregnancy in Patients with a History of CKD

There is increasing evidence indicating that a certain degree of renal insufficiency is associated with an increased risk for accelerated decline in renal function. Serum creatinine levels equal to or higher than 1.4 mg/dl (130 μmol/l) led to a more rapid progression of chronic renal failure in pregnant than in nonpregnant women with similar degrees of renal dysfunction [2, 9]. Considering patients with diabetic nephropathy, women with serum creatinine levels of 1.4 mg/dl (130 μmol/l) or greater, measured before pregnancy or in the first trimester, showed an accelerated progression of the renal disease [10]. Two studies showed that women with an initial serum creatinine level equal to or higher than 2 mg/dl (180 μmol/l) experienced a significant incidence of preterm delivery, preeclampsia and accelerated decline in renal function during or immediately after pregnancy [11, 12]. Imbasciati et al. [13] recently analyzed women with stages 3–5 CKD. No differences were found in the GFR before and after delivery in the entire cohort of women with a serum creatinine level of 1.5 mg/dl (140 μmol/l). Unlike this, an accelerated rate of GFR loss after delivery was observed in the subgroup of women with both an estimated GFR of 40 ml/min/1.73 m^2 and proteinuria of 1 g/day before pregnancy. These data clearly indicated that pregnancy should be avoided in this group. Therefore, in diabetic nephropathy and in other renal diseases, the level of renal function at the time of conception is pivotal to establish the possible effects on the progression of the disease. A very recent study also showed that the presence of CKD, as early as at stage 1, was associated with an increased rate of preterm delivery (44 vs. 5%), cesarean section (44 vs. 25%) and need for neonatal intensive care (26 vs. 1%). In addition, the authors demonstrated that the differences between the two groups were highly significant already at CKD stage 1 [14].

Hypertension

Hypertension is very common in conceiving women with renal disease [2]. In human pregnancy, hypertension has been associated with decreased uteroplacental blood flow. An animal model of hypertension in pregnancy nicely showed the presence of a 'pathogenic feedback' be-tween systemic hypertension and placenta, with alteration in the physiology of the fetus [15, 16]. By using an in vivo model, it has been demonstrated that maternal hypertension differentially alters placental structure and gene expression. The different grade of hypertension (mild or moderate) affected the placental functional capacity and, interestingly, contributed to programming of hypertension in adult offspring. In late gestation, the placental blood flow was significantly reduced in the moderate hypertension group, whereas mild hypertension resulted in an increase in placental efficiency, without significant changes in the placental blood flow. Profound alterations in the genes of the renin-angiotensin-aldosterone system were indeed identified [15, 16].

However, all antihypertensive drugs can be used to manage hypertension except ACE inhibitors or sartans. These drugs, which are frequently prescribed for their nephroprotective effect, appear to be related to an increased number of congenital malformations such as oligohydramnios, fetal growth retardation, neonatal death due to renal failure or hypotension [4, 17, 18]. There is no evidence that the possible suspension of these drugs during pregnancy can have an effect on the course of the maternal kidney disease.

Infections

Infections are common in women with renal disease during pregnancy. There is some evidence showing that the accelerated decline in renal function was triggered by urinary tract infections [2].

Preeclampsia

Preeclampsia is characterized by elevated blood pressure, proteinuria and edema, and complicates 5–8% of pregnancies [19, 20]. The risk factors for this condition are different, such as the advanced age of the mother, nulliparity, glomerulonephritis, diabetes, hypertension and obesity. Recent studies in patients have identified alterations in circulating angiogenic factors, in the renin-angiotensin system, and insulin resistance that might contribute to placenta ischemia [4, 21].

Studies of gene expression on the placenta from patients affected by preeclampsia indicated the presence of unbalanced expression between angiogenic and antiangiogenic factors [4, 22–24]. Molecules such as soluble fms-like tyrosine kinase 1 have been described to play a pivotal role in the endothelial dysfunction occurring in preeclampsia [21]. Interestingly, these new molecules have also been tested as candidate biomarkers for preeclampsia. However, despite the numerous independent

studies performed on these new potential biomarkers (placental growth factor in the first trimester; fms-like tyrosine kinase 1 or soluble endoglin in the second trimester), to date the screening for early detection of preeclampsia is still not possible in the clinical setting.

Up to now, little is known on the role of preeclampsia as a risk marker for subsequent end-stage renal disease. Vikse et al. [25] have recently analyzed a cohort of women who had had a first singleton birth between 1967 and 1991, including data from up to 3 pregnancies. They showed that among women who had been pregnant one or more times, preeclampsia during the first pregnancy was associated with a relative risk of end-stage renal disease of 4.7. These data, together with other interesting findings, demonstrated that preeclampsia is a marker for an increased risk of subsequent end-stage renal disease.

Despite several trials examining various interventions, no strategy has proven to be effective in the prevention or treatment of preeclampsia other than delivery of the fetus. Complications include maternal stroke, renal failure and placental abruption. Data in animal models indicated that the antagonism of vascular endothelial growth factor (VEGF) signaling by fms-like tyrosine kinase 1 occurs during preeclampsia. Gilbert et al. [26] demonstrated that chronic infusion of VEGF(121) during late gestation restored the GFR and endothelial function, decreasing the blood pressure associated with placental ischemia. Therefore, VEGF(121) may be a candidate molecule for the management of preeclampsia and its related complications.

Considering the drugs currently available, low-dose aspirin has been shown to have a small but significant effect on the prevention of preeclampsia [27]. This treatment seems to be safe and should be given to women who present risk factors for the development of preeclampsia. The dietary supplementation of calcium, folic acid or L-arginine has been suggested. However, randomized controlled trials are needed to support these initial observations [4].

Glomerulonephritis

A recent study by Limardo et al. [28] investigated the long-term outcome of kidney disease in women with IgA nephropathy and preserved kidney function, who did and did not become pregnant. As many as 223 women (136 and 87 in the pregnancy and nonpregnancy groups, respectively) had serum creatinine levels ≤1.2 mg/dl (110 μmol/l) at diagnosis. The results indicated that pregnancy in IgA patients did not affect the long-term outcome

of kidney disease. Similar results were reported in two studies showing that pregnancies in patients with Henoch-Schönlein purpura were complicated by proteinuria and/or hypertension, even in the absence of active renal disease [29–31].

Several studies investigated the effects of pregnancy in patients affected by systemic lupus erythematosus (SLE) [32]. Despite the great improvements in the survival of the mother and the fetus in the last few years, pregnant patients with SLE may still experience several complications. SLE is characterized by normal fertility that can be affected by treatment (e.g. cyclophosphamide) or by severe renal dysfunction. However, pregnancy in SLE patients is associated with thromboembolisms, fetal loss, hypertension, and preeclampsia [33]. Maternal mortality is more than 20-fold higher compared to the healthy population, with an odds ratio of 1.7 for cesarean section and 3.0 for preeclampsia [34, 35].

Renal flares in pregnant patients with SLE seem to occur in specific conditions, especially when active disease is present at the moment of conception [33, 36]. Another important factor to consider is the class of lupus nephritis. Classes III and IV are more associated with hypertension and preeclampsia compared to classes V and II [37]. The differential diagnosis of preeclampsia from a lupus flare is a major problem in pregnant SLE patients. As a first-line approach, autoantibody levels and analysis of urinary sediment should be performed to differentiate the disease. In addition, C3 and C4 levels, lupus anticoagulant and antiphospholipid antibodies should be tested. In fact, the presence of lupus anticoagulant is strongly associated with the development of preeclampsia.

The presence of hypertension, proteinuria, antiphospholipid syndrome and thrombocytopenia at the moment of conception is also associated with a poor fetal outcome in pregnant women with SLE [32]. With the improvement of therapeutic strategies over the last few years, fetal loss has decreased from 40% in 1960 to 17% in 2000 [33]. As a treatment that may help reduce such complications, acetylsalicylic acid was shown to lower the incidence of preeclampsia in SLE perinatal death with an increase in the birth weight [33].

Therefore, data from the literature suggest that the SLE activity should be monitored at least for 6 months before conception and that pregnancy should be started with no signs of active lupus nephritis. If these conditions are not present, then contraception should be strongly suggested to the patients.

Pregnancies in Dialysis Patients

Hemodialysis

Pregnancy is a challenge for women with end-stage kidney disease, especially for dialysis patients [38]. However, nowadays the massive improvements in maternal-fetal care and in dialysis efficiency, frequency, and support therapy allow them to reach previously inaccessible targets [1, 39]. There are few data about the conception rate for this population of women, and most of them are from old databases, spread in different countries. Data from the EDTA and national registries demonstrated a conception rate between 0.3 and 0.75/year/patient [40–43].

The analysis of these databases clearly showed that the rate of healthy newborn children, from women who are on dialysis, raised from 20–23% in the 1980s to 75% today, with an improvement also in the management of clinical problems [1, 14, 44, 45].

Outcome

Conception and positive outcome of the pregnancy are much more frequent when women have residual renal function, with a better prognosis for pregnancies that began before starting dialysis. Giatras et al. [46] observed that 47% of pregnancies in their population were successful during the first 2 years of dialysis, while women with 10 years of treatment had only 6 newborn babies out of a total number of 120 pregnancies.

Starting dialysis during pregnancy is related to a better fetus survival, almost 30% higher than the one observed in women under dialysis for years [42, 47]. There are some case reports of pregnancies in women with a 10-year history of dialysis [41, 48] but the birth of healthy newborns was extremely uncommon in these women [48, 49].

In light of the heterogeneity of the data coming from the literature, any attempt to correlate outcomes with dialysis therapy is hazardous; however, the best results are reported in settings of long daily dialysis, suggesting that dialysis efficiency may play an important role [50–52]. Recent evidence showed that after the 16th–20th week, the cumulative dialytic dose should be increased from 3 sessions/week to daily treatments. A better outcome, for the fetus, was reached with 24–28 h of dialysis per week [53].

In 2004, Gangji et al. [54] reported a case where conventional hemodialysis was switched to nocturnal hemodialysis in a patient with uncontrolled hypertension. The pregnancy ended with a natural delivery of a healthy, '38-week-old' infant. In 2005, Haase et al. [52] presented

their observations on women treated with an intense hemodiafiltration protocol of 24–36 h/week with improved fetal outcomes. Also, Barua et al. [50] reported their successful results on nocturnal home hemodialysis. This therapeutic indication for long-lasting dialysis is confirmed by the actual literature [14] and allows the physicians to manage, in a better way, some clinical issues related to these kinds of pregnancies like hypertension and polyhydramnios [2, 4, 50, 54–56].

Despite the progressive improvements, in about 50% of pregnant women on dialysis pregnancies do not end with the birth of a healthy child, and neonatal mortality is higher than the one observed in the general population, with a higher rate of early delivery, a mean gestational time of 32 weeks and a lower weight at birth [14, 53, 57, 58].

Malnutrition

Data from the literature indicate that malnutrition is particularly common in pregnant hemodialyzed women. For this reason, it is necessary not to limit the daily calorie intake to 1.2–1.3 g/kg/day of proteins. Particularly, there is the need of 1 g/kg related to a sufficient mother intake and a supplementary one of 20 g/day necessary for a correct development of the fetus [2, 59]. Some authors even suggest a 1.8 g/kg/day protein intake [46]. According to these suggestions there are some case reports about intradialytic hyperalimentation as adjuvant support in pregnant hemodialysis patients [60].

Peritoneal Dialysis

Peritoneal dialysis is characterized by a lower rate of pregnancies, about 50–70% less than the one observed in the hemodialysis population, with important issues related to the maintenance of a good nutritional asset [61, 62]. Despite the low number of pregnancies, peritoneal dialysis seems to have a better outcome if compared to hemodialysis with a higher rate of live newborn babies. This result may be related to residual renal function and to the less traumatic and more paraphysiologic depurative action of peritoneal dialysis [63].

Pregnancy in Transplantation Patients

KDIGO guidelines suggest that women should not become pregnant at least 1 year after transplantation. In addition, pregnancy should only occur if kidney function is stable with a proteinuria lower than 1 g/day. For a successful pregnancy, the history of renal dysfunction is also

important: a serum creatinine level greater than 1.5 mg/dl before transplantation is related to an increased risk of irreversible graft loss during pregnancy [2]. Moreover, this risk of graft loss is lower with a better renal function at the time of conception [59, 64–67]. Other experiences suggest a deleterious effect of pregnancies on graft function in patients with a serum creatinine level of 1.75 mg/dl (160 μmol/l) and a greater risk for patients with a pre-pregnancy creatinine level of 200 μmol/l [68]. There is a consensus that waiting more than 2 years after transplantation ensures a better graft survival [68]. However, there are pregnancies even during the first year after transplantation [69].

There are different clinical complications related to a pregnancy after solid organ transplantation. According to the data presented by the National Transplantation Registry in 2004, hypertension is reported with a rate from 47 to 73% in women during pregnancies which occurred after kidney transplantation [70]. The mean birth weight of infants of mothers receiving calcineurin inhibitors (CNIs; cyclosporine and tacrolimus) is reported to be 2.1–2.5 kg with a mean gestational time of 35 weeks instead of 37 weeks observed in CNIs-free immunosuppressive protocols. Hypertension occurring in this population might explain these data, and may require a more aggressive treatment [70–73].

Preeclampsia also seems to be related to the low birth weight, the reduced duration of gestation and the increased risk of developing hypertension. Almost one third of pregnant women receiving a kidney or combined kidney-pancreas is reported to develop preeclampsia [70]. According to medical indications, deliveries are more likely to be performed by cesarean section [73].

Immunosuppression and Pregnancy in Kidney Transplant Recipients

The most challenging part of the follow-up during pregnancy is tailoring the immunosuppressive strategy. There is the experimental evidence that mTOR inhibitors are embryotoxic or fetotoxic in rats [74]. Recent studies suggest a pivotal role for mTOR inhibitors in embryo implantation [75]. According to the literature, mTOR inhibitors should be stopped or replaced before pregnancy with azathioprine (KDIGO 2009). Data from the National Transplantation Pregnancy Register showed 2 patients, whose therapy with sirolimus was switched to azathioprine during the first trimester, and who gave birth to children in the 36th and the 38th week of gestation with a birth weight of 2,637 and 3,076 g, respectively, while 2 cases of pregnancies without discon-

tinuation ended with spontaneous abortions in the 8th and 6th week [76].

Few data are found in the literature about female recipients with sirolimus exposure during pregnancy; Guardia et al. [75] reported a successful pregnancy under sirolimus-based immunosuppression [77, 78]. Due to this shortness of data related to controlled studies in women, mTOR inhibitors are categorized as 'C' by the FDA [73].

A first look at the outcomes in CNI-treated female kidney transplant recipients with an interval from transplant to pregnancy greater than 5 years showed a favorable risk profile for the newborn, the recipient and the graft. There were no maternal or fetal deaths, no rejection was observed during pregnancies and serum creatinine levels remained stable during and after pregnancy. The only negative evidence, compared to the normal population, was a higher incidence of spontaneous abortion (23.5 vs. 16%) [79].

Reducing the risk of rejection is possible by keeping appropriate blood levels of CNIs. According to data reported in the National Transplantation Pregnancy Register, pregnant kidney transplant recipients who maintained stable function during their pregnancies took higher doses of cyclosporine before and during pregnancy than patients who had renal dysfunction [80]. Based on the use of tacrolimus, Jain et al. [79] reported 21 pregnancies with decreased trough levels for kidney and kidney-pancreas recipients with no rejection episodes. Available reports indicate a similar rejection rate between the transplant recipient population with and without pregnancies [70, 82].

There is a higher concern for the safety of the child. CNIs cross the placenta entering the fetal circulation [83] and there is evidence that fetus trough levels are half the mother's ones [84, 85]. It is obvious that there is the possibility of fetotoxic and teratogenic effects. All the data collected in the literature came from observational studies in humans and evaluation of the gestation in rodents.

CNIs are not related to any pattern of congenital malformations in rodents and there is evidence of growth delay, cataracts and fetotoxic effects at high doses [56, 74, 86]. Regarding structural malformations in children of transplant recipients receiving CNIs, the incidence of malformations remains low and the prevalence of major structural malformations is similar to that in children of healthy women [87]. Taking into account the available data, CNIs received the 'C' class category by the FDA because human risk cannot be ruled out, since studies on humans are lacking and studies on animals are either positive for risk or lacking evidence [73].

The same 'C' class category is assigned to mycophenolate mofetil, in both its formulations, by the FDA [73]. The KDIGO recommendation is to stop or replace mycophenolate mofetil before pregnancy is attempted. The European Best Practice Guidelines in 2002 suggested stopping mycophenolate mofetil 6 weeks before the attempt to conceive. This suggestion was given according to data, revealed by manufacturers, about structural malformations in offspring of animals exposed to mycophenolate mofetil during pregnancy [82]. In 2004, Le Ray et al. [74] reported the case of a newborn whose mother received mycophenolate mofetil during pregnancy developing multiple malformations similar to the ones observed in animal models [80]. A 2006 report of 18 kidney recipients observed 26 pregnancies under mycophenolate mofetil with 11 spontaneous abortions, 15 children with malformations including hypoplastic nails and shortened fingers, microtia with cleft lip and palate, microtia alone and neonatal death with multiple malformations [84].

A 2008 report suggested the hypothesis that utero exposure to mycophenolate mofetil can cause a characteristic phenotype and suggests the existence of a mycophenolate-associated embryopathy, whose main features are: cleft lip and palate, microtia with atresia of external auditory canal, micrognathia and hypertelorism. Ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations and diaphragmatic hernia may be part of the phenotypic spectrum of this embryopathy [88–90].

Future Perspective for Pregnancy in CKD

In conclusion, it is important to consider that most of the literature on this topic includes a single center, is retrospective, and uncontrolled, especially for the measurement of renal function. Moreover, data on pregnancy outcomes are missing on specific renal diseases.

Despite these limits, we have to recognize the increasing evidence that the degree of renal insufficiency, rather than the underlying renal diagnosis, is the primary determinant of outcome. In the presence of CKD, especially in glomerulonephritis such as SLE, the nephrologist should be aware of the high risks for renal loss, pregnancy complications, preterm delivery and uterine growth retardation.

Therefore, we think that the report of any pregnancy in specific registries may not only be useful but necessary to develop our knowledge and achieve successful medical management of the mother and the infant in the presence of CKD.

Acknowledgement

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