Review

An Overview on Dialysis on Pregnancy

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Abstract： Background: Pregnancy rates in women on dialysis have increased in the last decades, thus making it a topic of growing interest. The rarity of this event is predominantly due to fertility problems and to the high rates of pregnancy failure including stillbirth, fetal and neonatal deaths [1]. Methods: We conducted a narrative review of existent literature in order to analyse the major issues about pregnancy on dialysis to give the reader a full updated prospective about this topic which, even if not common, is becoming more and more frequent. Results: Even if recently acquired knowledge has improved diagnosis and treatment of dialysis pregnancies focusing on several aspects, pregnancy on dialysis remains a great challenge for obstetricians and should be managed by a multidisciplinary expertise team. Conclusion: Dialysis in pregnancy may be necessary for women previously affected by end stage renal disease (ESRD) becoming pregnant, or in case of acute renal injury presenting for the first time during gestation or, again in case of existent renal pathology worsening during pregnancy and requiring dialysis. Although some evidence suggests that more intensive dialysis regimens are correlated with better obstetric outcomes, the optimal therapeutic protocol still remains to be established.

Keywords: Dialysis in pregnancy; End stage renal disease; Haemodialysis; Peritoneal Dialysis; Intensive Dialysis regimen; Preeclampsia

INTRODUCTION

Pregnancy in women on dialysis is not common, but is becoming increasingly topical. The rarity of this event is predominantly due to fertility problems and to the high rates of pregnancy failure including stillbirth, fetal and neonatal deaths [1]. Moreover, the majority of women with renal insufficiency pursue pregnancy at more advanced ages and can be afflicted by underlying diseases [2]. Therefore, these women represent a population of high risk-patient, with increased rates of adverse pregnancy outcomes, including abortion, preeclampsia, preterm delivery, fetal growth restriction, low birth weight and higher frequency of neonatal intensive care unit admissions [3]. Women with advanced stages of Chronic Kidney Disease (CKD) may also have further deterioration of kidney function after pregnancy [1].

Since the first successful case of pregnancy on haemodialysis described in 1971 by Confortini et al. [4], the incidence of pregnancies complicated by CKD is becoming more and more frequent and increasingly being encountered in obstetrical practice. It is estimated that CKD affects about 3% of pregnant women in high-income countries, and its prevalence will further grow, due to advanced maternal age and obesity [5]. Literature evidence suggests a six-fold increase of the number of dialysis pregnancies from the years 2000-2008 compared to the years 2008-2014 [6]. This increment of cases could be related to improved medical care, in particular intensive dialysis regimens, better blood pressure control, adequate maternal nutrition with supplementation of iron, vitamins, folic acid and erythropoietin, and the multidisciplinary monitoring [7].

Despite renal transplantation for women with ESRD offers better perspectives to reach improved pregnancy outcomes [8], we should highlight that, even if complicated to manage, pregnancy on dialysis is achievable, although it is still high-risk.

MATERIALS AND METHODS

Data from PubMed, Scopus and Medline electronic databases were used to review existing literature about pregnancy on dialysis. We included studies from the past 20 years using keywords such as "pregnancy dialysis", "chronic kidney disease pregnancy", "end stage kidney disease pregnancy", "kidney disease in pregnancy", "renal disease in pregnancy", "maternal renal disease".

We included randomised controlled trials (RCT), retrospective studies, cohort studies, non-inferiority trials, narrative and systematic reviews, case reports. Studies not sufficiently focused on the topics discussed and in unknown languages were excluded.

FERTILITY

First of all, it is well known that women with ESRD frequently experience reduced fertility. It has been hypothesized that the decline of glomerular filtration rate (GFR) and uremia leads to dysregulation of the hypothalamic-pituitary-ovarian axis [9]. In fact, constantly increased luteinizing hormone (LH) levels lead to loss of cyclical hormones variability and absence of mid-cycle LH surge, with suppression of ovulation [10]. Moreover, impaired renal clearance of prolactin and resulting high circulating levels of this hormone contribute to ovulation failure [11]. Sexual dysfunction is also usual in these patients manifesting as reduced libido, dyspareunia, altered body image and depression [12].

Some aspects of dialysis treatment in ESRD seem to be crucial to achieve a successful pregnancy. Jesudason et al. found that conceiving before dialysis, even if dialysis is commenced and continued during pregnancy, is related to highest live birth rates compared to dialysis already established at conception (91% versus 63%; P=0.03) [13]. This is probably due to the residual renal function in patients who conceive before dialysis, which, on the contrary, often declines in women already subjected to dialysis [14,15].

PREGNANCY DIAGNOSIS AND MANAGEMENT OF EARLY GESTATION

Because of irregular menstrual periods, pregnancy is not easy to detect in the early phases in women with ESRD and the diagnosis is often delayed at about 16.5 weeks of gestation [15]. Beta hCG levels are unreliable, since always increased in dialysis patients, even in non-pregnant ones. Therefore, the safest method to confirm pregnancy and calculate gestational age is ultrasound assessment [16]. Because of decreased renal clearance, besides beta hCG, also maternal serum PAPP-A levels are increased in women on dialysis, therefore non-invasive screening is not appropriate and should be not recommended. Moreover, the performance of cell free DNA testing in this type of population is not well known [17]. During prenatal counselling, the health-care provider should advise these women that invasive prenatal screening is the only reliable method to detect fetal genetic abnormalities. However, rates of fetal malformations in mothers with renal failure seem comparable to those seen in the general population (approximately 2%), except for diabetic nephropathy, hereditary diseases and use of teratogenic drugs [6].

DIALYSIS TECHNIQUE: PERITONEAL DIALYSIS AND HAEMODIALISYS

Dialysis during gestation may be necessary for various causes. There is the possibility of a pre-existent renal pathology worsening during pregnancy and requiring dialysis, or the condition of women previously affected by ESRD becoming pregnant, but acute renal injury could also present for the first time during gestation [18]. In literature, no differences regarding maternal and fetal outcomes between haemodialysis (HD) and peritoneal dialysis (PD) are reported [19], and none of the techniques seems to influence negatively the infant survival rate [20]. Nevertheless, it is necessary to specify that literature data on PD are limited, probably because of the lower diffusion in the general

population of this technique compared to HD and because pregnancy rates are lower in this group of patients. The mechanism supposed to be involved is that intraperitoneal hypertonic solutions may be associated with inflammatory effects on the fallopian tube and the uterus, interfering with embryo implantation [3].

In case of acute or rapidly progressive chronic renal disease, the most important management choice to do is when to start the treatment. There are no specific values beyond which is mandatory to start dialysis, and validated methods for the assessment of residual renal function in pregnancy do not exist [3]. Nevertheless, it is clear that the dialysis treatment should begin earlier in pregnant patients and generally should be considered for values of serum creatinine of 3,5-5,0 mg/dl and for GFR <20 mL/min [21,22]. Clinicians may also consider commencement of dialysis when urea is >17mmol/L [23], because fetotoxicity of urea is more important than any maternal indication to begin dialysis [3].

There is no clear consensus in literature on the most appropriate dialysis technique (HD or PD) to start in case of acute renal injury presenting for the first time during gestation.

Data reported in literature on HD are much richer than those on PD because of the higher number of patients on HD and the good pregnancy outcomes reported. Nevertheless, there is only one author, Vazquez, in 2010 clearly reporting HD as the first choice in pregnant women or postpartum period complicated by acute renal insufficiency or in case of worsening of renal function at the time of conception [24]. However, it is reasonable to think that HD, being the most frequently used technique, is therefore the most suitable one in case of acute renal injury occurring for the first time in pregnancy, especially considering the acute technical difficulties associated with peritoneal dialysis treatment (positioning and maturation of the Tenchkoff catheter).

In pregnant women already on dialysis there is no indication to change dialysis technique, as suggested by the Italian Study Group on Kidney and Pregnancy in 2015 [16]. The recommended strategy is that treatment regimens should be intensified to achieve better gestational outcomes, so to reduce interdialytic weight gain and fetal exposure to harmful substances [18].

Intensive dialysis regimens are associated with higher conception rates and have a positive correlation with pregnancy outcomes, including gestational age and birth weight, having an influence on placental development that is crucial for fetal well-being [25]. Retrospective data demonstrate that more intensive dialysis schedule, increasing the number of hours from <20 to >36 hours per week, is associated with regularization of menstrual cycles, better neonatal outcomes and live birth rate growth from 48 to 85%, with a positive dose response ratio [25].

There are several advantages of intensive HD in pregnancy. Intensive HD facilities excess fluid removal so there is less variation in intra-dialytic blood pressure [25], allows better control of blood pressure so reducing the use of antihypertensive agents and diuretics [24,25] compared to standard dialysis (≤20 h/week), and also increases clearance of uremic toxins that improves pregnancy outcomes [25].

High biocompatibility dialysers are recommended [24] because a lower surface area avoids excessive fluid loss with less episodes of hypotension and changes in osmolality [26].

Although there are several risks of pregnancy-related complications, also intensive PD regimens can be used and do not induce metabolic changes also allowing a gradual fluid control, so controlling blood pressure [15]. However, PD could negatively influence maternal nutrition status and could require lower dialysate volumes because of overdistension of uterus in the late trimester of pregnancy [22].

NUTRITION

Intensive dialysis regimens require attention on maternal nutritional status because of higher risk of adverse perinatal outcomes. Literature data recommend energy requirements related to pre-gestational weight, adding pregnancy energy needs and weight gain during the trimesters. For pregnant women under dialysis, the Italian study group suggests adding 146.4 kJ/kg (35 kcal/kg) during HD and 104.6 kJ/kg (25 kcal/kg) during PD to diet. These doses have to be calculated considering pre-gestational weight, and must be added to the standard pregnancy energy

requirement for each trimester [27]. It is also recommended to control interdialytic weight gain. The Italian study group suggests that protein intake for HD and PD should be 1.2 and 1.4 g/kg/day of pre-gestational weight, respectively, thus avoiding early preterm delivery, very low birth weight and SGA infants [27].

Dialysis in pregnant women is associated with hydroelectrolytic imbalance, and dosage adjustments of potassium, sodium and calcium are required. Intensive dialysis promotes vitamins elimination [15], so vitamin C, thiamine, riboflavin, niacin and vitamin B may be supplemented [2]. Placenta converts calcidiol into calcitriol, thus 25-OH vitamin D must be measured every trimester, and it may be integrated if is necessary [22]. Iron deficiency anemia is correlated with adverse perinatal outcomes, like preterm birth, LBW, and SGA newborns [28]. Anemia is higher in pregnant women on HD compared to women on PD [19], therefore patients should receive supplemental oral iron and folic acid. Prescription of erythropoietin (Epo) may be necessary, with no increase in blood pressure or teratogenicity [24].

MATERNAL OUTCOMES

Pregnancy in dialysis is burdened by several adverse outcomes: miscarriage, anaemia, infection, polyhydramnios, premature rupture of membranes, preterm birth, hypertension and superimposed preeclampsia or eclampsia, increased haemorrhagic risk, and maternal death.

Hypertension is very common and preeclampsia (PE) occurs in up to 40% of pregnant women with CKD. This risk increases with increasing stage of CKD and is ten-fold higher compared to women with normal renal function [1,29]. Superimposed preeclampsia is difficult to diagnose in patients with underlying kidney disease, because, as a recent cohort study reveals, standard diagnostic criteria cannot be applied in 75% of women (45 out of 60) [30]. Hypertension and proteinuria are pre-existing the pregnancy in the majority of cases. Anuria in patients with ESRD does not allow using as a means of diagnosis neither proteinuria nor impaired renal function. Assessment of angiogenic markers (the ratio of soluble FMS-like tyrosine kinase-1: placental growth factor - sFLT1: PlGF), which is now emerging as predictor of PE in the general obstetric population, is limited in women with CKD [31]. The research of adequate markers of PE in these women is still matter of study. In 2013, Piccoli et al. suggested abnormal uterine and umbilical arteries pattern flow at Doppler evaluation combined with fetal growth restriction as indicators of PE in women with CKD [32]. A retrospective cohort study, published in 2018, highlighted that higher residual renal function was negatively related to the risk of onset of PE in these patients [33].

Antihypertensive drugs commonly used for hypertension during pregnancy include alpha-methyldopa, nifedipine, and labetalol. Uncontrolled hypertension must be quickly and adequately controlled, the target of blood pressure to achieve is below 140/90 mm Hg while hypotension (<120/70 mm Hg) should be avoided [34]. Normal blood pressure, in fact, influences fetoplacental circulation and reduces the risks of fetal loss, stillbirth and intrauterine growth restriction [35]. Patients requiring multidrug treatment for blood pressure control and with poorly controlled hypertension are at higher risk of adverse pregnancy outcomes [36].

In a 2008 descriptive cohort study, dialysis regimens seemed to influence positively hypertension pathogenetic mechanisms, with intensive HD improving endothelial function [37]. On the contrary, a recent national online survey performed by Sachdeva et al. found that women who received HD >20 hours weekly were 2.2 times more likely to develop preeclampsia than those who received HD 20 hours per week. They hypothesised that intensive HD regimens entails an increased vasoconstriction due to tighter volume control [38].

If severe preeclampsia occurs or preterm delivery <32 weeks' gestation has to be planned, magnesium sulphate is indicated both for preeclampsia-associated seizure prophylaxis and fetal neuroprotection. Literature suggests using magnesium sulphate at lower dosage in patients on dialysis, typically without a maintenance infusion, because of its renal clearance. Careful monitoring of vital parameters is also recommended [34].

FETAL OUTCOMES

Preterm delivery and intrauterine fetal growth restriction are common in patients with ESRD on dialysis. Commonly, preterm birth in these patients is often medically indicated and rarely a result of spontaneous preterm labour [39]. However, cases of cervical shortening and cervical incompetence are described [25,40,41] and might be related to the decreased levels of progesterone [42]. It is estimated that preterm birth occurs in about 80% of new-borns, with a median gestational age in the range of early preterm delivery (33-32 weeks or less) [6,15].

The new-borns tend to have a low weight; the incidence of SGA neonates in ESRD patients is estimated at about 50% [43]. According to a 2016 case report analysis of a systematic review, the incidence of SGA on HD is lower as compared to PD (31 versus 66.7%; P = 0.015) [6]. Furthermore, the same review highlighted that dialysis frequency (number of dialysis sessions per week) was related to the incidence of SGA neonates and that dialysis duration (weekly hours of dialysis) was significantly related both with preterm delivery and SGA neonates, with better results obtained improving dialysis regimens [6].

Another common complication in pregnant woman on dialysis is polyhydramnios. It is estimated that it can occur in about 30-70% of the pregnancies [43], even if the exact pathogenesis is not well known. It is speculated that urea-rich urine and the related osmotic diuresis lead to increased fetal urine production. To reduce osmotic fetal diuresis, some studies suggest increasing the HD dosage to facilitate the maternal uremia decrease and consequently fetal blood urea levels [15,19]. However, the evidence of polyhydramnios is strictly related to normal fetal renal blood flow and therefore might represent an indirect marker of an adequate placental perfusion [34-44].

Maternal monitoring also includes the evaluation of anemia, probably due to erythropoietin resistance, which is often associated with high transfusion rate in these patients [44].

CONTRACEPTION

Health-care providers should offer contraceptive and pre-pregnancy counselling to these patients. Even though fertility is reduced, mainly due to the prevalence of anovulatory cycles, pregnancy is possible in all CKD stages, including transplantation and dialysis [45]. Clinicians should advice women of reproductive age with ESRD about the possibility of contraception, if pregnancy is not desired. Unwanted pregnancy may impact not only psychologically, but also clinically on these patients, leading to complications for mother and fetus. Progestogen only methods are safer because of the reduced side effects in patients at a high risk of thromboembolism and hypertension. Medicated or non-medicated intrauterine devices are good contraceptive options in CKD patients, but contraindicated in patients on peritoneal dialysis [46].

PRE-PREGNANCY COUNSELLING

Preconception counselling in women with ESRD is vitally important and should include all the information to optimize health before pregnancy. They should receive extensive counselling regarding the risks related to their particular disease and kidney function. These patients should be advised that pregnancy should be postponed in the case of active immunologic diseases and that the exposure to teratogenic drugs should be avoided. They also should be assisted in managing correctly other comorbidities, like diabetes and systemic lupus erythematosus [47].

These women should also be aware that kidney function, before pursuing pregnancy, might determine the success or failure of the gestation. According to a 2019 review [47], serum creatinine (Scr) levels before pregnancy relates to maternal and fetal outcome, in fact, Scr < 1.4 mg/dL is associated with positive event whereas Scr =1.4-2.9 mg/dL defines a higher risk for pregnancy complications. Moreover, levels of Scr ≥ 3.0 mg/dL seem to be related to deterioration of renal function once pregnancy is solved.

CONCLUSIONS

Pregnancy rates in women on dialysis have increased in the last decades but these patients still represent a population of high-risk. All women on dialysis in pregnancy should be managed by a multidisciplinary team because of high risk of adverse pregnancy outcomes, both maternal and fetal,

including hypertensive disorders, preterm birth, low birth weight. An adequate pre-pregnancy counselling is recommended and a management by specialist in maternal-fetal medicine, nephrologist, neonatologists, nurses, midwifes and dieticians is necessary. There are no guidelines or established protocols on this topic, but literature evidence suggests a direct correlation with intensive dialysis regimens and better pregnancy outcome than the past. So, even if complicated to manage, pregnancy on dialysis is achievable, although it is still high-risk.

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