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Pregnancy and End-Stage Renal Disease

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Abstract
Pregnancy is uncommon in women with end-stage renal disease (ESRD). Fertility rates are low in women on dialysis, and physicians still frequently counsel women with ESRD against pregnancy. Advancements in the delivery of dialysis and obstetric care have led to improved live birth rates in women on dialysis, so pregnancy for young women with ESRD is now more feasible and safer. However, these pregnancies remain high-risk for both maternal and fetal complications, necessitating experienced multidisciplinary care. In this article, we review fertility issues in women with ESRD, discuss pregnancy outcomes in women on dialysis, and provide an approach for management of pregnant women with ESRD.

Introduction

Pregnancy is uncommon in women with end-stage renal disease (ESRD). Fertility rates are low in women on dialysis, and physicians still frequently counsel women with ESRD against pregnancy. Advancements in the delivery of dialysis and obstetric care have led to improved live birth rates in women on dialysis, so pregnancy for young women with ESRD is now more feasible and safer. While transplantation remains the best option for many women with ESRD desiring pregnancy, pregnancy on dialysis is now an option for women who are unlikely to get a kidney transplant during their reproductive years. In this article, we will review fertility issues in women with ESRD, discuss pregnancy outcomes in women on dialysis, and provide an approach for management of pregnant women with ESRD.

Fertility and ESRD

Fertility in women with CKD diminishes as the glomerular filtration rate declines, with menstrual cycle irregularities developing in many women once the glomerular filtration rate is below 15 mL/min [1]. Once reaching end-stage disease, most women are anovulatory, even if regular menstruation is present [2], as uremia leads to dysregulation of the hypothalamic-pituitary-gonadal axis. Follicular stimulating hormone levels are similar to non-uremic women, but luteinizing hormone (LH) levels are elevated. Additionally, lack of cyclic LH release

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leads to the absence of the LH surge necessary for ovulation [3]. Estradiol and progesterone are decreased in uremic women, which can result in uterine atrophy [4]. Reduced prolactin clearance by the kidneys also results in hyperprolactinemia, further inhibiting ovulation [5]. Women with ESRD may undergo menopause earlier (median age 47) versus the general population (median age 51 years), but it is unclear if this is a true or a functional state of menopause [1]. Sexual dysfunction also contributes to low pregnancy rates in women on dialysis. Among women on hemodialysis, 84% reported sexual dysfunction and only 35% of women reported being sexually active [6]. Depressive symptoms, medications, anemia and negative body image (potentially related to the presence of catheters and fistulas) contribute to low libido [7].

Kidney transplantation rapidly reverses the neurohormonal abnormalities and improves libido leading to improvements in fertility [8, 9]. Whether or not intensified dialysis regimens improve the hormonal aberrations and sexual dysfunction associated with ESRD has not been adequately studied. There is, however, some suggestion that more intensive dialysis can improve prolactin levels and restore regular menses, thereby increasing the likelihood of conception [10]. As such, contraception counseling remains important in women of childbearing age undergoing intensive dialysis.

Pregnancy Incidence

Hemodialysis

The exact rates of pregnancy on hemodialysis are difficult to quantify due to inconsistent methods in ascertainment and reporting from registry data. Although historically thought to be a very unlikely occurrence, there is more contemporary data to suggest pregnancy on dialysis is becoming more common. Data from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry confirm that pregnancy rates, while currently low, appear to be increasing. Prior to 1976, there were no reported pregnancies in the registry, with rates increasing to 0.67 pregnancies per 1,000 person-years from 1986 to 1995 and to 3.3 pregnancies per 1,000 person-years in 1996–2008 [11]. A recent meta-analysis noted a large increase in number of reported cases of pregnancy in women on hemodialysis (616 pregnancies from 2000 to 2014) [12] compared with a similar review completed less than a decade earlier (90 from 2000 to 2008) [13]. This increase may reflect more intensified hemodialysis regimens (use of high flux membranes, nocturnal therapy), increased use of erythropoietin or a change in counseling practices. However, increased clearance is likely a contributing factor, given the experience from Toronto, where 7 out of 45 women receiving intensive dialysis became pregnant. All these women were previously on conventional hemodialysis and had not conceived, suggesting dialysis time and clearance are likely important factors [14].

Peritoneal Dialysis

Pregnancy rates in women on peritoneal dialysis (PD) are lower than on hemodialysis. In the largest survey on pregnancy and ESRD from the United States, 1.1% of reproductive age women on PD conceived versus 2.4% on hemodialysis [15]. Data from the ANZDATA Registry also reported lower conception rates in women on PD compared to hemodialysis (1.06 vs. 2.54 pregnancies per 1,000 patient-years) [11]. The etiology of the lower rates of conception in women on PD remains unclear, especially in the United States, where PD patients are generally healthier and have higher residual renal function than women on hemodialysis. A hypothesis is that hypertonic dextrose solutions and the fluid filled peritoneum interfere with ovum transit to the uterus [16]. These theories are hypothetical, and it remains unclear if women on PD should be counseled to switch to hemodialysis if they wish to conceive, but it is our practice in Toronto to initiate or switch young women to an intensified hemodialysis regimen if a pregnancy is desired.

Pregnancy Outcomes

Hemodialysis

Live birth rates in pregnant women on hemodialysis are improving. In the United States, live birth rates were 37% in the 1980s, improving to 52% for pregnancies occurring after 1990 [17]. More recent data from centers using intensified hemodialysis regimens during pregnancy report live birth rates greater than 80% [18–20]. The benefit of intensified dialysis was highlighted in a study comparing pregnancy outcomes from 21 pregnancies from the Toronto Pregnancy and Kidney Disease (PreKid) Clinic and Registry (2000–2012) with 71 pregnancies in the American Registry for Pregnancy in Dialysis (1990–2011) [20]. The Canadian cohort received significantly more dialysis (43 ± 6 vs. 17 ± 5 h per week) and had a live birth rate of 82 vs. 53% in the US cohort.

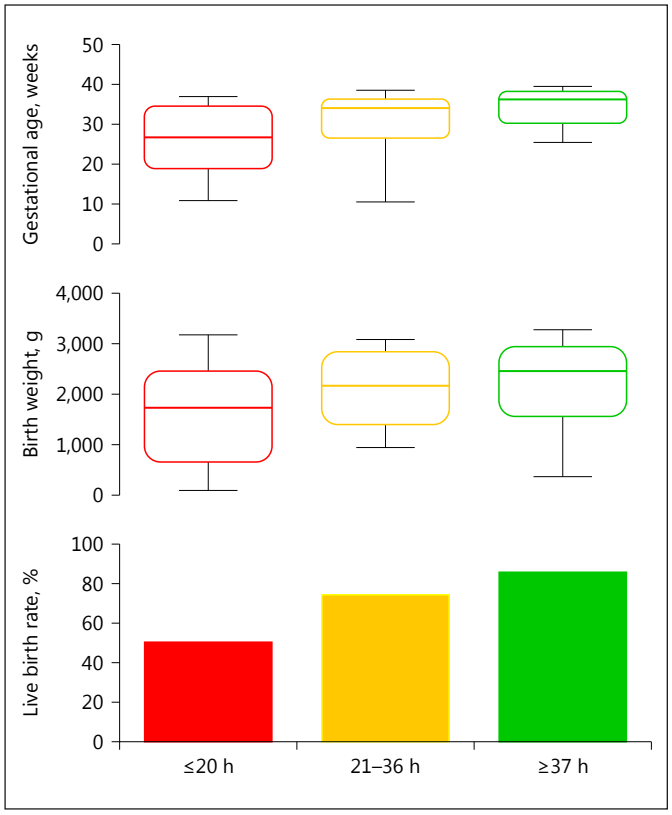

Fig. 1. Gestational age at delivery, offspring birth weight and live birth weight by the number of weekly hours of hemodialysis (HD) in a Canadian and American cohort. Adapted with permission from [20].

When stratified by dialysis time, the live birth rate was 48% in women receiving 20 h of hemodialysis per week or less and 85% in women receiving 36 h of dialysis per week or more. The duration of pregnancy was longer in the Canadian cohort at 36 weeks compared to 27 weeks in US patients with trends toward higher birth weights (Fig. 1) [20].

The encouraging results from intensified dialysis protocols have led to the widespread adoption of intensified dialysis regimens in pregnant women. To quantify the relationship between time on dialysis and pregnancy outcomes, Piccoli et al. [12] performed a meta-analysis of existing observational studies that included 681 pregnancies in 647 women. The analysis concluded that longer weekly dialysis times were associated with lower rates of preterm delivery and small for gestational age offspring. Most interestingly, the effect of dialysis time appeared continuous without an identified threshold effect of therapy [12], but there was a paucity of data between 20 h and the recommended minimum of 36 h per week routinely delivered in Toronto, so the precise dose needed to optimize outcomes remains unclear.

Women who initiate dialysis during pregnancy have improved outcomes compared with those who conceive on dialysis. It is hypothesized that the presence of residual renal function in the former group is protective. In a study from the ANZDATA Registry, live birth rates were 91% in women who conceived before dialysis initiation compared to 63% in those who conceived on dialysis, as there were significantly higher rates of early pregnancy losses in established dialysis patients [21].

Despite the above-mentioned improvements in live birth rates for women on hemodialysis, there is still risk for significant morbidity to both mother and offspring. Early reports demonstrated high rates of maternal morbidity, including severe uncontrolled hypertension, preeclampsia, hemolysis, elevated liver enzymes and low platelets syndrome as well as the need for frequent blood transfusions [22]. Women managed with intensified hemodialysis have improved blood pressure control and lower transfusion requirements [19, 20]. Estimating the rates of maternal hypertensive disorders of pregnancy such as preeclampsia is difficult, as there is no standard definition of preeclampsia in the dialysis population. Offspring of mothers with ESRD have higher rates of prematurity, growth restriction, polyhydramnios, and stillbirth [17, 23]. In the aforementioned meta-analysis of dialysis schedules and pregnancy outcomes, rates of maternal death were low (0.4%) and the rates of fetal malformations were the same as in the general population (approximately 2%) [12].

Peritoneal Dialysis

Data on pregnancy outcomes in women on PD are limited and most often case reports [24–26]. Case series are infrequent and many do not include women who were on PD prior to conception [27]. There are several complications that are unique to PD including exit site infections, catheter malposition and drainage difficulties, polyhydramnios, and peritonitis [28–30]. Catastrophic complications such as placental abruption and uterine trauma from the PD catheter have been reported [30, 31]. Preterm deliveries, premature rupture of membranes, and stillbirth have been reported in association with acute peritonitis [31, 32]. Again, the recent comprehensive meta-analysis, which also included PD, noted a significantly higher rate of small for gestational age babies as compared to babies born on hemodialysis (67 vs. 31%; p = 0.015) [12].

Table 1. Management of pregnant women on hemodialysis

Medication management
Discontinue teratogenic medications (ACE inhibitors, ARBs, statin)
Double dose of water soluble vitamins
Add folic acid 5 mg/day
Consider low-dose aspirin for preeclampsia prevention
Dialysis Prescription
Increase dialysis time: if no residual renal function, >36 h. If residual renal function, time tailored to individual metabolic parameters with goal pre-HD BUN <50 mg/dL
Increase dialysate potassium concentration to 3 mEq/L
Increase dialysate bath calcium concentration to 3 mEq/L (1.5 mmol/L)
Sodium phosphate to dialysate or oral supplementation to maintain serum phosphorus levels if necessary
Blood pressure and volume
Target BP <140/90 mm Hg post-dialysis
Frequent clinical volume assessments to avoid intradialytic hypotension and manage ultrafiltration volume
Anemia
Intravenous iron to maintain optimal iron stores
Erythropoietin-stimulating agent to target hemoglobin 10–11 g/dL
Diet
Daily protein intake of 1.5–1.8 g/kg/day
Unrestricted diet including liberalized dietary phosphate
Fetal Surveillance
First trimester screening to exclude Down Syndrome including ultrasound measurements of nuchal translucency, amniocentesis or cell-free DNA tests
Ultrasound to measure cervical length and assess for fetal anomalies at 18–20 weeks
Placental ultrasound with Doppler assessment at 22 weeks
Weekly ultrasound and BPP from 26 weeks until delivery
Planned induction after 37 weeks where appropriate
Postpartum
Medication review to ensure that all medications are compatible with breastfeeding
Avoid volume depletion to facilitate breastfeeding
Preservative-free heparin to avoid neonatal toxicity from benzyl alcohol
Maternal emotional support

Management of the Pregnant Patient on Hemodialysis

Significant changes in dialysis care are required when managing a pregnant woman on hemodialysis (Table 1). A multidisciplinary team, including nephrologists, high-risk obstetricians, neonatologists, nurses, pharmacists, social workers, and dieticians are essential for optimal care. Nephrological management involves the intensification of dialysis dose, management of electrolytes, volume status, anemia, and bone care. Obstetric care is concentrated on optimization and surveillance of fetal well-being and growth.

Early Pregnancy Management

Pregnancy diagnosis on dialysis is difficult, given that menstrual irregularities and amenorrhea are common. This can result in a delayed pregnancy diagnosis. Clinicians should discuss the potential for pregnancy in all young women with ESRD of childbearing age and maintain heightened surveillance, given the teratogenic medications often prescribed to this patient population. Commonly used teratogenic medications in the dialysis population are angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Both classes of medications are associated with significant teratogenicity if continued beyond the first trimester and should be discontinued immediately [33]. Initial care includes discontinuation of teratogenic medications with substitution for pregnancy-safe options.

Standard first trimester pregnancy screening tests must be interpreted with caution in women with ESRD. Beta-human chorionic gonadotropin is partially cleared by the kidneys and inversely correlated with creatinine

clearance [34]. Pregnancy-associated plasma protein-A levels are higher in patients on hemodialysis and levels are increased by the administration of heparin [35, 36]. As such, Down syndrome screening requires confirmation by an ultrasound measurement for nuchal translucency, cell-free chromosomal microarray tests or amniocentesis.

Supplementation of water-soluble vitamins and minerals, including folic acid, is essential in early pregnancy. Folic acid, which is required for neural tube closure, is cleared by high-intensity hemodialysis. Many centers advocate for double the daily dose of water-soluble vitamins, including a minimum of 5 mg folic acid [37]. In women with kidney disease, low-dose aspirin is recommended for the prevention of preeclampsia [38]. There is no data on the effectiveness of aspirin in women with ESRD. The concurrent use of heparin may increase the risk of bleeding. If used, aspirin can be stopped between 34 and 36 weeks in anticipation of delivery.

As mentioned above, there is evidence that increased dialysis intensity improves pregnancy outcomes in women with ESRD. Increasing dialysis time is associated with increased live birth rates as well as lower rates of premature delivery and fetal growth restriction [12, 20]. As there appears to be no "threshold" effect for this benefit, we recommend 36 h a week minimum in women with ESRD, but women with significant residual renal function may not need this intensified therapy and therapy should be tailored to a woman's individual needs.

Intensified hemodialysis allows for easing of dietary restrictions required during conventional hemodialysis therapy. Nutritional counseling is important to ensure adequate protein intake. Recommended protein intake for pregnant women is 1.1 g/kg/day. Because 10–15 g amino acids can be lost daily in the dialysate, higher intake (1.5–1.8 g/kg/day) is recommended [39]. Dialysate potassium concentration can be increased to 3.0 mEq/L as necessary, and phosphate binders can typically be discontinued. Further, phosphate supplementation is often necessary orally or by addition of sodium phosphate to the dialysate. Calcium bath concentration should be increased to ensure adequate calcium for fetal skeletal development, especially in the third trimester, and vitamin D analogs are considered safe in pregnancy. There is very limited experience with calcimimetic use in pregnancy.

Anemia is common among pregnant women with ESRD. Erythropoiesis-stimulating agent (ESA) requirements increase during pregnancy and IV iron is needed to maintain normal iron saturation [39]. Hemoglobin goals should approximate the physiologic anemia of pregnancy (10–11 g/L). ESAs do not cross the placenta and are considered safe in pregnancy [40]. Iron sucrose is the preferred form of intravenous iron during pregnancy.

Late Pregnancy Management

Fetal surveillance in the second and third trimesters includes serial assessments of fetal growth and monitoring of cervical competency and amniotic fluid levels. Cervical incompetence appears to be more common in women with ESRD compared to the general population [20]. Cerclage may be necessary to prevent preterm delivery among women with ESRD on intensive hemodialysis. Polyhydramnios may be secondary to inadequate clearance of uremic toxins (elevated BUN results in fetal diuresis) or volume overload. The presence of polyhydramnios should prompt an increase delivered dialysis dose or an increase in ultrafiltration volume. Volume management during pregnancy is challenging because dry weights are difficult to ascertain. Dry weight increases throughout pregnancy by up to 0.5 kg/week during the second and third trimesters. Frequent clinical assessments of volume status are the best way to determine ultrafiltration targets.

Hypertension is a common medical comorbidity in women with ESRD. Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, are difficult to diagnose in this population because there are no standard diagnostic criteria [41]. Hypertension usually improves with intensified dialysis, and therefore worsening hypertension after 20 weeks of gestation should raise the concern for superimposed preeclampsia. Slowing fetal growth, new fetal growth restriction and alterations in placental Doppler blood flow are also more suggestive of placental causes of hypertension [42]. It is too early to know how to incorporate novel biomarkers of preeclampsia (soluble Flt-1, placental growth factor) as diagnostic tests for preeclampsia in women on hemodialysis [43–45].

Delivery should take place in a center with neonatal intensive care facilities, given higher rates of preterm delivery. There is no contraindication to a vaginal delivery in women on hemodialysis, and caesarean section should be reserved for the usual obstetric indications. In pregnancies with no evidence of maternal or fetal complications, patients are often induced at 37 or 38 weeks of gestation. In women who develop signs and symptoms of severe preeclampsia, special precaution must be taken when administering intravenous magnesium sulfate for seizure prophylaxis given its mechanism of clearance. Magnesium toxicity, which can result in muscle weakness, hypotension, and respiratory depression, is treated by urgent dialysis.

Postpartum

There are no known contraindications to breastfeeding in women with ESRD on hemodialysis. ACE inhibitors may be used post-partum for women who benefit from renin-angiotensin-aldosterone system blockade for blood pressure management. Captopril, enalapril, and quinapril are the preferred ACE inhibitors to use in the post-partum period as they are absent in breast milk [46]. ESAs and iron can be continued. Preservative-free heparin should be used as the additive benzyl alcohol can be toxic to preterm infants [47]. Emotional support is also essential: many new mothers can no longer manage home-based dialysis and need to temporarily transition to in-center therapy.

Management of the Pregnant Patient on PD

The above-mentioned management strategies for hemodialysis patients can be applied to management of the pregnant patient on PD. Women with significant residual renal function should be able to achieve adequate clearance with standard PD prescriptions. Increasing dialysate volume and/or the number of exchanges can be used to intensify PD dose. However as pregnancy progresses, the uterus limits larger exchange volumes [26]. Frequent exchanges via continuous ambulatory PD or continuous cycling PD or addition of hemodialysis to supplement PD clearance are often used [25, 28, 48].

Conclusions

Successful pregnancy is possible for young women with ESRD during their reproductive years. Intensive dialysis has led to improved live birth rates; however, these pregnancies remain high-risk and require multidisciplinary care, given high rates of preeclampsia, cervical incompetence, preterm delivery, and small for gestational age offspring in this population. Further, the need for emotional support of these vulnerable young women cannot be understated because both the commitment necessary to carry a pregnancy on intensive dialysis as well as face the challenges associated with raising a child can prove to be extremely daunting for a young woman with a chronic illness.

Disclosure Statement

The authors have no disclosures related to this work.

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