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Dialysis in pregnancy

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A B S T R A C T

Although kidney disease impacts on fertility, increasing numbers of pregnancies are reported in women on dialysis. Despite a trend of increasing live birth rates over recent decades, pregnancies on dialysis remain high risk with increased rates of adverse pregnancy outcomes including pregnancy loss, pre-eclampsia, pre-term delivery, low birth weight and higher levels of neonatal care. This article describes the prevalence of dialysis and pregnancy in women of childbearing age, with relevant information regarding the effects of end-stage renal disease on fertility in women. Pregnancy outcomes for women on dialysis are summarised, including their association with dialysis intensity. A guide to pre-pregnancy counselling, and the management of pregnancy on dialysis is provided. Factors that inform the decision to commence dialysis in pregnancy are examined. The advantages and disadvantages of peritoneal dialysis in pregnancy are discussed.

Dialysis and pregnancy in women of childbearing age

The number of women of childbearing age receiving dialysis varies according to healthcare provision and renal disease incidence. In the United Kingdom, the prevalence of dialysis in women of childbearing age (18–45 years) is 150 women per million population, with the most prevalent underlying diagnoses being glomerulonephritis and diabetic nephropathy [1,2]. For women receiving dialysis, reproductive healthcare options and outcomes are dictated by the effect of end-stage renal disease on both fertility and pregnancy.

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The overall incidence of pregnancy in women receiving dialysis remains low; estimated to be 1% of that in the population [3,4]. However, since the first report of a live birth in a woman receiving haemodialysis was published in 1971 [5], increasing rates of pregnancy in women on dialysis are described. The Australian and New Zealand Dialysis and Transplantation (ANZDATA) registry reported pregnancy rates of 0.54 per 1000 person years from 1976 to 1985, 0.67 from 1986 to 1995, and 3.3 from 1996 to 2008 [6]. Similarly, a systematic review of dialysis in pregnancy identified 90 cases between 2000 and 2008, compared to 584 pregnancies in the years 2008–2014 [7]. Although publication bias cannot be excluded, a six-fold increase in literature is strongly suggestive of an increasing incidence of pregnancy in women on dialysis. Improved obstetric surveillance, blood pressure control, the availability of erythropoietin stimulating agents, a change in the clinician-approach to pregnancy in chronic kidney disease, and the use of intensive dialysis regimens may be important contributing factors.

Fertility and dialysis

The impact of end-stage renal failure on fertility is likely to be multifactorial. Impaired renal function impacts the hypothalamic-pituitary-ovarian axis leading to an inverse relationship between glomerular filtration and fertility [4]. Ovulation is usually triggered by a surge in the concentration of leutenising hormone (LH) at the mid-point of the menstrual cycle, driven by the positive feedback of oestrogen to the hypothalamus-pituitary. However, in women with advanced chronic kidney disease oestrogen concentrations are low leading to negative feedback to the hypothalamus, and although LH concentrations are increased [8] there is a loss of variability and the mid-cycle surge [9] meaning ovulation fails to occur. In addition, there is impaired renal clearance of prolactin [9,10], which mimics the physiological effect of breast-feeding and confers additional suppression of ovulation. Treatment with cyclophosphamide, which is used in the treatment of rapidly progressive glomerular disease is known to be gonadotoxic and may contribute to infertility in previously exposed women. Small cohort studies show that 42% of women on dialysis have a regular menstrual cycle, compared to 75% prior to the start of dialysis [11], and 37–59% of women on haemodialysis are amenorrhoeic [11,12]. Importantly, kidney disease is also associated with non-mechanistic sexual dysfunction including reduced libido, dyspareunia, negative body image and depression, even before the need for dialysis arises [13,14].

Pregnancy rates in women receiving peritoneal dialysis are less well described in published literature, but appear lower than rates on haemodialysis. ANZDATA shows pregnancy rates of 1.06 pregnancies per 1000 patient years in women on peritoneal dialysis, which is significantly less than the haemodialysis rate of 2.54 [6]. This has led to conjecture that the use of intraperitoneal fluid may be associated with mechanical or inflammatory effects on the fallopian tube and/or uterus, in addition to the mechanistic, endocrine effects of renal impairment.

Although end-stage renal disease impairs fertility, it should not be considered a reliable form of contraception as unplanned pregnancies do occur. There is emerging evidence that this may be particularly relevant for women receiving an increased number of hours of dialysis. Increasing haemodialysis provision from 16.5 to 28 hours per week in a small cohort of seven women was associated with return of menses in amenorrhoiec women, and intensifying treatment to 36 hours of dialysis per week (from 12 hours) in a single centre led to conception rates of 15.6% (7 out of 45 women), which is 10 times greater than that reported by national registries [15,16].

The provision of safe and effective contraception is essential for women on dialysis who do not wish to conceive. However, for women on dialysis (and those with CKD) contraceptive advice and provision remain inadequate [4]. There is limited guidance on contraception for women on dialysis, and safety data [17] are generalised from other high-risk groups. Effectiveness must consider the failure rate with the ‘typical-use’ of contraceptive methods as discrepancies exist compared to ‘perfect-use’ [18]. For example, the ‘typical-use’ of condoms leads to 18–21% of couples experiencing an unintended pregnancy in the first year of use, compared to 2–5% with perfect use. This means that with typical use, condoms are an unacceptable long-term option for couples that wish to avoid pregnancy. Progesterone based methods avoid the risks associated with oestrogen use; namely hypertension, vascular disease, lupus flare, thromboembolism and cervical cancer. Progesterone-only methods are therefore considered safe for women on dialysis [19] and include the progesterone-only pill, the intra-uterine system

(Mirena®) and the progesterone implant (Nexplanon®), with typical use failure rates of 9%, 0.5% and 0.02% respectively [18]. The copper coil is a safe and effective non-hormonal based method. Progesterone-only emergency contraception can be provided to women on dialysis up to 72 hours after unprotected sexual intercourse.

Pregnancy outcomes on haemodialysis

Population studies [20], large cohorts [21], and meta-analysis [22] show that chronic kidney disease confers an increased risk of adverse pregnancy outcomes including pregnancy loss, pre-eclampsia, pre-term delivery, small-for-gestational-age babies, increased neonatal care requirements and perinatal death. Absolute risk rates vary between studies and are affected by cohort size, the timing and method by which renal function is measured, and clinician thresholds for iatrogenic delivery and neonatal intensive care admission. However, a consistent finding is the increment in risk with worsening CKD stage and the highest rates of adverse outcomes for women on dialysis.

Rates of adverse pregnancy outcomes for women on dialysis are shown in Table 1. This table demonstrates an increase in the live birth rate of babies born to women on dialysis over the last 30 years, although a high prevalence of pre-term delivery and low-birth weight babies remain consistent findings. Synthesis of data from published cohorts since 2000 equates to a live birth rate of 78% (range 61–89%), at a mean gestational age of 34 weeks (range 27–35 weeks), with 46% of babies being small for gestational age (range 14–80%). Rates of pre-eclampsia are heterogeneous. The difficulty in making a diagnosis of superimposed pre-eclampsia in the clinical context of pre-existing hypertension and/or proteinuria/anuria is a likely contributing factor (see: Obstetric management). Where there has been an attempt to standardise the diagnosis of superimposed pre-eclampsia rates are 14–19% in women on dialysis [23,24] (Table 2).

Numerous cohort studies demonstrate a trend of improved pregnancy outcomes with longer dialysis time in pregnancy [23,25–31]. This is most convincingly shown in a Canadian cohort of 22 women with established end-stage renal disease who received 43 ± 6 hours of dialysis per week during pregnancy. This was associated with a significantly higher birth rate (83% versus 53%) and increased gestational age (36 versus 27 weeks), compared to the provision of 17 ± 5 hours of dialysis per week [30]. Meta-analysis of data from 2000 to 2014 showed that dialysis frequency and dialysis duration show an inverse correlation with rates of preterm delivery and small for gestational age infants [7], although data heterogeneity prevents stratification by other potentially important factors including maternal age, renal disease aetiology and the level of residual renal function. A recent large Brazilian case series of women receiving haemodialysis during pregnancy between 2000 and 2017 included 47 women with established end-stage renal disease and 46 women with new dialysis requirements in pregnancy [23]. Multivariable modelling of these data showed that midweek blood urea nitrogen was significantly associated with gestation-adjusted fetal weight, although the development of pre-eclampsia remained the most important factor in predicting adverse pregnancy outcome. However, it is worthy of note that recent cohorts reporting a relationship between the intensity of dialysis provision and pregnancy outcome do so in clinical settings which include an expert multidisciplinary team, close maternal (weekly) and fetal (fortnightly) surveillance, early pre-eclampsia prophylaxis and appropriate blood pressure, electrolyte and anaemia management [23,30].

Pre-pregnancy counselling for women on dialysis

The aim of pre-pregnancy counselling is to facilitate informed, value congruent choice for women and their partners. It is advocated for all women with a pre-existing medical condition given the identification of maternal mortality in women who do not receive pre-pregnancy advice [32]. Although maternal risk in CKD is comparable to the general population, there is a significantly increased risk to the babies born to women on dialysis including fetal growth restriction, preterm delivery and an 18% risk of perinatal death [7]. However, CKD does not remove the innate longing to have a child and the patient experience of physicians' warnings against pregnancy in CKD can be traumatic [33]. Neither CKD nor the need for dialysis should negate the autonomous decision to undertake a pregnancy, but autonomy is only possible with a full understanding of the implications of kidney disease for pregnancy

Table 1
Summary of published literature examining dialysis provision and outcomes in pregnancy in chronological order. Studies included in systematic reviews [7,64] are not listed separately with the exception of [30], which is an important comparative cohort study of intensive dialysis in pregnancy. Values are mean unless otherwise stated.

Study	Study details	Number of pregnancies	Dialysis details	Definition of pre-eclampsia	Pregnancy outcomes
Souqiyyeh et al., 1992 [25]	Questionnaire (Saudi Arabia)	27 HD	Longer dialysis in pregnancies >28 weeks gestation	NA	• BP/pre-eclampsia: not available • Gestational age: 74% < 34 weeks • Live birth rate: 37% • Birthweight: not available
Hou 1994 [65]	Questionnaire (US)	19	Not available	NA	• BP/pre-eclampsia: not available • Gestational age: 95% preterm • Live birth rate: 37% (52% after 1990) • Birthweight: not available
Bagon et al., 1998 [26]	National survey (Belgium)	15 HD	Correlation between birth weight and dialysis dose	NA	• BP/pre-eclampsia: not available • Gestational age: 100% preterm • Live birth rate: 50% for established HD, 80% if new HD in pregnancy • Birthweight: 100% low birthweight
Okundaye et al., 1998 [27]	Questionnaire (US)	245 HD 59 PD 40 unknown	Trend to better survival with dialysis >20 h/week	NA	• BP: 79% > 140/90, 48% > 170/110 • Gestational age: 32.4 weeks (84% < 37 weeks) • Live birth rate: 42% • Birthweight: 28% ≤ 10th centile
Romão et al., 1998 [66]	Retrospective cohort (Brazil)	14 HD 3 PD	HD 15–18 h/week, PD 6 × 2L/day Mean urea 28 mmol/L	Not defined.	• Hypertension or pre-eclampsia: 47% • Gestational age: 32.3 weeks • Live birth rate: 79% HD, 33% PD • Birthweight: 1401 g
Toma et al., 1999 [38]	Questionnaire (Japan)	74 HD	Target urea <21 mmol/L, mean 22 h/week	NA	• Severe hypertension: 42% • Gestational age: 31.9 weeks (87% < 37 weeks) • Live birth rate: 49% • Birthweight: 1544 g (93% < 2500 g, 31% < 1000 g)
Asamiya et al., 2009 [29]	Retrospective cohort (Japan)	28 HD	Mean HD time: • T1: 12.7 h/week • T2: 15.9 h/week • T3: 18.4 h/week Negative correlation between BW and urea	NA	• Hypertension: 39% • Gestational age: 92% preterm • Live birth rate: 64% • Birthweight: 42% small for dates
Piccoli et al., 2010 [64]	Systematic review of published literature 2000–2008	90 86 HD 4 PD	HD 15–40 h/week	No standardised definition between included studies.	• BP/pre-eclampsia: 20–66% • Gestational age: 67–100% preterm • Live birth rate: 76% • Birthweight: 1390–2418 g (FGR 14–80%)

Hladunewich et al., 2014 [30]	Retrospective cohort comparison of intensive (Canada) and conventional HD (US)	22 intensive HD 70 conventional HD	Intensive HD: 43±6 h/week Conventional HD: 17±5 h/week Dialysis intensity correlates with birth rate and gestation	Not available.	• Severe hypertension or pre-eclampsia: 9% (intensive) • Gestational age: 36 weeks (intensive), 27 weeks (conventional) • Live birth rate: 86% (intensive), 61% (conventional) • Birthweight: 2118 g (intensive), 1748 g (conventional)
Piccoli et al., 2016 [7]	Systematic review of published literature 2000–2014, extension of [64], includes [28].	35 HD start after conception 58 conception after HD start 14 PD	HD: 18–36 h/week PD: 5–6 × 1.5 L	Lack of standardised definition between included studies.	• Hypertension 48–63%, pre-eclampsia 5–14% • Gestational age: HD = 33 weeks, PD = 34 weeks • Live birth rate: 82% • Birthweight: Conception before HD = 1804g (SGA 17%), HD before conception = 1700 g (SGA 33%), PD = 1780 g (SGA 57%)
Jesudson et al., 2014 [59]	Retrospective cohort (Australia and New Zealand)	63 22 conceived before dialysis, 41 conceptions on dialysis (34 HD, 7 PD)	Not available	Database definition at the discretion of reporting clinician.	• BP/pre-eclampsia: 15% • Gestational age (median): 34 weeks (11% < 28 weeks) • Live birth rate: 73% (82% after 20 weeks) • Birthweight (median): 1750 g (50% ≤ 10th centile)
Sachdeva et al., 2017 [31]	Internet based survey of practice (USA)	187	Most common prescription 24–27h/week. 66% aim for pre-dialysis urea <17.9 mmol/L. More live births with dialysis >20 h/week	Not available.	• Pre-eclampsia: 44% • Gestational age: not available • Live birth rate:78% • Birthweight: not available
Luders et al., 2018 [23]	Retrospective cohort (Brazil), extension of previously published data [67]	93	2000–2008: 9–18 h/week depending on urine output, > or < 1year of HD, and body weight. 2009–2017: Target midweek urea <12.5 mmol/L	BP > 140/90 after 20 weeks and new/doubling of proteinuria >300mg/24 h and systemic manifestations/FGR with abnormal placental Doppler waveform.	• Pre-eclampsia: 14% • Gestational age: 35 weeks • Live birth rate: 89% • Birthweight: 1689 g (SGA 48%)
Normand et al. [24]	Retrospective cohort (France)	100	Mean HD time: •T1 14.6 h/week •T3 20.5 h/week Mean urea: •T1 17.0 mmol/L •T2 13.4 mmol/L	Proteinuria >300mg/24 h plus any of elevated LFTs/thrombocytopenia/pulmonary oedema of no other cause	• BP/pre-eclampsia: 18.8% • Gestational age: 33.2 weeks • Live birth rate: 78% • Birthweight: 1719 g (45% < 10th centile)

HD = haemodialysis, PD = peritoneal dialysis, BP = blood pressure, FGR = fetal growth restriction, LFT = liver function tests, SGA = small for gestational age, T1 = first trimester, T2 = second trimester, T3 = third trimester, NA = not applicable.

Table 2
Pre-pregnancy checklist for women on dialysis: modifiable risk factors in advance of pregnancy.

Factor	Details
Blood pressure	• Aim for BP < 140/90
Medication	• Use of angiotensin blockade (ACEi/ARB) prior to conception is dependent upon the strength of the indication for angiotensin blockade and the likelihood of early detection of pregnancy. Angiotensin blockade can be continued until conception provided there is regular pregnancy testing during attempts to conceive. • Medications which are safe to continue in pregnancy include labetalol, nifedipine, methyldopa, aspirin, unfractionated and low molecular weight heparins, intravenous iron, and synthetic erythropoeitin. • There are limited published safety data on amlodipine. • Stop statins when pregnancy is confirmed. • Optimise parathyroid function in advance of pregnancy. Discontinue cinecalcet when pregnancy confirmed.
Dialysis	• Plan for the provision of increased dialysis during pregnancy • Discuss conversion from peritoneal dialysis to haemodialysis for pregnancy • Ensure adequate dialysis access with fistula formation prior to pregnancy for women on maintenance haemodialysis.
Supplements	• Prescribe folate 5 mg daily (due to increased losses with both HD and PD [67]) for ≥12 weeks prior to conception for fetal neural tube formation. • Treat vitamin D deficiency
Co-existing conditions	• Diabetes: pre-pregnancy HbA1c is associated with pregnancy complications. Aim for fasting blood glucose <7 mmol/L, HbA1c < 48 mmol/mol (6.5%) but avoid problematic hypoglycaemia. • Lupus: quiescent disease for 6 months prior to pregnancy. • Genetic counselling for inherited conditions.
Other	• Weight reduction for increased BMI • Confirm rubella immunity and vaccinate in advance of pregnancy if required • Stop smoking

ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, BP = blood pressure, HD = haemodialysis, PD = peritoneal dialysis.

and therefore the provision of expert, individualised pre-pregnancy counselling is essential. The challenges of undertaking a pregnancy on dialysis for women and their care-givers, as well as the very real possibility of parenting a small, sick neonate must be effectively communicated. The use of absolute numbers, rather than the use of relative terms including ‘high’ and ‘low’ risk is advocated. To date, there is no decision-aid available for women with CKD that has been shown to facilitate involvement in clinical decision-making and improve risk perception with regards to pregnancy.

The risks of pregnancy following successful kidney transplantation are less than those for women on dialysis. The possibility of a lower-risk pregnancy in the future should therefore be considered, although this is dependent upon the likely timing of transplantation within the reproductive age window, graft stability at >1 year and the use of immunosuppressive regimens compatible with pregnancy. Parenthood in the absence of pregnancy can be achieved by surrogacy and adoption, although the validity of these options for women on dialysis depends upon legal, ethical, and cultural factors, which vary across the world. In the UK, adoption is not a service for infertile or high-risk women but a service for children, who often have complex parenting needs. It requires a detailed approval process, including consideration of the time commitment of dialysis, the capacity of partners and family to provide parenting support in the event of deteriorating maternal heath, and prognosis within childhood.

Pre-pregnancy counselling strives to optimise maternal health in advance of pregnancy. A pre-pregnancy checklist including relevant modifiable risk factors is provided (Table 2). Women should be empowered to understand and optimise their health and manage their medication prior to and at the diagnosis of pregnancy. Given the association between longer dialysis time and improved neonatal outcome (see: Pregnancy outcomes on haemodialysis) and concern regarding intensification of peritoneal dialysis (see: Peritoneal dialysis), a plan should be made for increased provision of haemodialysis in the event of pregnancy. Vascular access should be adequate for the treatment requirements of pregnancy, and women on maintenance haemodialysis should have a fistula formed in advance of pregnancy whenever possible.

The management of pregnancy in women established on haemodialysis

Published data on dialysis in pregnancy is limited by cohort size and clinical heterogeneity. Randomised controlled trial evidence is unlikely to inform the management and intensification of dialysis in pregnancy due to the rarity of the condition and the ethical difficulties in randomisation given a perceived lack of clinical equipoise, and clinicians uncomfortable with the provision of less than 6-times-weekly dialysis for women with established renal failure in pregnancy [34]. Clinical guidance is therefore based on low and moderate levels of evidence, generalisation of evidence from non-CKD cohorts, and expert consensus. However, levels of evidence defined by traditional hierarchies should not lead to presumptions about quality. Clinical experience and multidisciplinary working are difficult to quantify for the purposes of intervention research but such factors are thought to contribute to improved pregnancy outcomes in women on dialysis [16,23,30]. Antenatal care should take place within an expert, collaborative multidisciplinary team including obstetricians, nephrologists, fetal medicine specialists, neonatologists, nurses, midwifes and dieticians; acknowledging the essential support that is provided by partners and family. The clinical value of expert consensus statements from such groups should not be underestimated.

Diagnosing pregnancy

Diagnosis of pregnancy is difficult in end stage renal disease due to the fact that irregular menstrual cycles and amenorrhea are common in women on dialysis (see: Fertility and dialysis), and urine volumes may be insufficient for standard pregnancy tests. In addition, the kidney plays a key role in the metabolism of beta-human chorionic gonadotrophin (β-HCG). Reduced parenchymal and excretory function is thought to contribute to the detection of elevated serum concentrations β-HCG in 8–16% of non-pregnant women with CKD [35,36]. The sensitivity and specificity of a relative rise in β-HCG for the diagnosis of pregnancy in CKD remain unknown. Verification and dating of pregnancy by ultrasound imaging is therefore recommended [37].

Haemodialysis management for established end-stage renal failure in pregnancy

Intensive (>36 h/week) haemodialysis in pregnancy facilitates ‘gentle’ excess fluid removal with less variation in intra-dialytic blood pressure, better blood pressure control and improved fetal outcomes compared to standard dialysis (≤20 h/week) [15,30]. A continuous association between increased dialysis provision and improved fetal outcomes is shown at >20 h/week [27,28,31] and >36 hours per week [30]. Expert consensus from Italy suggests 36 hours as a minimum target for haemodialysis provision in pregnancy for women established on dialysis prior to pregnancy [37].

An alternative approach uses the serum urea concentration to guide the intensification of dialysis. Retrospective survey data suggests better pregnancy outcome at urea thresholds of <21 mmol/L [38] and <17.9 mmol/L [31]. A large contemporary cohort of 93 pregnancies showed that a midweek pre-dialysis blood-urea-nitrogen >35 mg/dl (urea >12.5 mmol/L) had a sensitivity of 88% and an odds ratio of 6.4 (CI: 1.4–30.0) for adverse fetal outcome [23]. With increasing recognition of the value of intensive dialysis in pregnancy, recommended targets for pre-dialysis urea concentration in pregnancy have shown a progressive decline from <17 mmol/L [37], to 10–15 mmol/L [16], to <12.5 mmol/L [23]. The use of a target serum urea concentration potentially facilitates individualisation of dialysis intensification in pregnancy, allowing for adjustment according to residual renal function. This is also relevant for women newly commenced on dialysis (see: Commencing haemodialysis in pregnancy).

Establishing an appropriate dry-weight for dialysis requires expert clinical examination including an appreciation of the normal haemodynamic changes of pregnancy (‘a hyperdynamic hyperhydrated state’ [37]), aiming for a post-dialysis blood pressure <140/90 mmHg whilst avoiding intra-dialytic hypotension (<120/70 mmHg) [16]. Weight gain due to pregnancy is estimated to be 300–500 g/week during the second and third trimesters and should be accommodated appropriately in dialysis weight targets [37,39]. Low molecular weight and unfractionated heparin can be safely used in pregnancy to prevent clotting of the haemodialysis circuit, although doses may need to be increased in pregnancy. For women receiving an intensified daily dialysis regimen in pregnancy there may be a need to use increased dialysate concentrations of potassium (3mEq/L), calcium (1.5 mmol/L), and phosphate (Fleet® enema added to the dialysis bath) [16]. Serum magnesium concentration may also fall with intensive dialysis and oral supplementation may be required, particularly given the association of low serum magnesium concentration with both hypertensive disorders of pregnancy [40] and uterine contraction [37]. There is no evidence that aneurysmal dilatation of fistulae is more likely in pregnancy, nor that a specific needling technique is associated with better long-term functionality post-partum. Best evidence from the non-pregnant population is therefore generalised to fistula management in pregnancy.

Erythropoietin concentrations approximately double in physiological pregnancy in the absence of CKD [41] and a similar increase in synthetic erythropoietin dose should be anticipated pregnancy to maintain haemoglobin levels at 100–110 g/L [16]. Iron deficiency is common in pregnancy and the safe intravenous use of iron sucrose, iron dextran and ferric carboxymaltose are described in pregnancy, although there is a paucity of published data examining exposure in the first trimester [42]. However, in the absence of any evidence of teratogenicity, expert consensus is that intravenous iron should not be withheld from women on dialysis in early pregnancy. Vitamin D deficiency should be corrected for all pregnant women, including the use of activated analogues for women on dialysis. Calcimimetic drugs are discontinued given the limited data on their use in pregnancy. Depending on the amount of dialysis provided in pregnancy, it is common to be able to discontinue phosphate binders. If phosphate binders are indicated, calcium is safe for use in pregnancy, although sevelamer is usually avoided due to animal evidence of impaired ossification of the fetal skeleton at supra-therapeutic doses [43].

Obstetric management

All women who require, or who may require, dialysis in pregnancy have a high risk for adverse pregnancy outcomes and should be referred in early pregnancy for consultant-led obstetric care. Recommendations for the obstetric management of pregnant women on dialysis are based on case series [15,30], expert opinion [16,37,44] and the generalisation of good quality evidence from other high-risk groups [45,46]. The obstetric management of women on dialysis is detailed in Table 3.

Meta-analysis demonstrates that women with CKD have a ten-fold higher risk for the development of pre-eclampsia compared to women with normal renal function [22], and statistical modelling of retrospective cohort data shows that the development of pre-eclampsia is the most important factor in predicting adverse pregnancy outcome in women on dialysis [23]. However, the diagnosis of pre-eclampsia is complicated in women with CKD, including those on dialysis. A diagnosis of pre-eclampsia is based on *de novo* development of hypertension after 20 weeks gestation in association with proteinuria and/or evidence of systemic disease (maternal acute kidney injury, liver dysfunction, neurological features, haemolysis, thrombocytopenia, or fetal growth restriction) [47]. Such definitions are rendered redundant for the majority of women on dialysis who may have chronic hypertension, variation in blood pressure according to fluid state, pre-existing proteinuria and/or anuria. Standardised definitions of superimposed pre-eclampsia in women with CKD do not exist. Weekly [16] maternal clinical assessment for maternal systemic signs and symptoms of pre-eclampsia and fortnightly [23,30] surveillance of fetal growth and well-being are therefore mandatory after 20 weeks for pregnant women on dialysis.

Fetal surveillance in women on dialysis involves fortnightly assessment of fetal growth after 20 weeks gestation in conjunction with Doppler ultrasound assessments of flow in uterine and umbilical arteries [23,30]. A small prospective study of 15 women with hypertension and/or CKD has demonstrated that increased vascular resistance in the uterine artery at 20–24 weeks gestation has 100% specificity for the development of superimposed pre-eclampsia [48], although this requires validation in a larger cohort including women on dialysis. Progressive changes in the waveform in the umbilical artery are used in the assessment of fetal distress and inform decisions regarding iatrogenic preterm delivery. Data from 61 women with CKD suggest that the combination of uterine and umbilical flow patterns can be used to distinguish CKD, which is associated with normal flow, from superimposed pre-eclampsia where flow velocity waveforms are abnormal [49].

Table 3
Obstetric management of women on dialysis, adapted from Refs. [37,39]. This should occur in addition to standard obstetric care including anomaly screening, lifestyle advice, vaccination, delivery and breastfeeding information, mental health screening and support.

Pregnancy stage	Management	Additional information
All	Individualised care plan, manage as high-risk.	Coordination of appointments with times on dialysis
	Target blood pressure <140/ 90 mmHg (post-dialysis)	Blood pressure may vary according to fluid state between dialysis sessions. Avoid hypotension (<120/70 mmHg) on dialysis.
Early	Early referral for consultant-led care	Surveillance and management should occur in the context of an expert multidisciplinary team.
	Pre-eclampsia prophylaxis with low dose aspirin (75–150 mg)	High quality data for high-risk women in general obstetric population [45,46].
	Pre-eclampsia prophylaxis with calcium supplementation	Indicated for women with calcium deficiency [68], although this likely to have been managed in advance of pregnancy in women known to nephrology services. Supplementation should be limited to 1.5g/day in women on dialysis as per CKD guidelines.
	Trisomy screening	No increased trisomy risk associated with CKD and dialysis. Elevation of β-HCG and PAPP-A in CKD may affect screening results. Consider non-invasive testing based on circulating fetal DNA if available.
	Folate supplementation	Increased prophylactic dose (5 mg daily) due to increased losses on dialysis.
Middle	Increased fetal surveillance	No outcome data related to different schedules of care. Expert consensus: fetal growth and well-being assessment 2–4 weekly from 24 weeks, with more frequent assessment if clinically indicated including waveform abnormalities or any clinical concern regarding possible superimposed pre-eclampsia.
	Cervical length	Increased rates of cervical shortening (18%) in recent published cohort of women on dialysis [30]. Significance and role of cerclage unknown.
End	Magnesium	Maintenance doses given for eclampsia prophylaxis/treatment or fetal neuroprotection should be omitted or reduced. Clinical monitoring for toxicity is required, as serum levels may not predict clinical effect. Aim for serum concentration <3.5 mmol/L. Toxicity should be managed with dialysis.
	Delivery	Timing of delivery is based on maternal and fetal wellbeing. Elective induction of labour may be considered at 37 weeks to allow for planning of dialysis and the need for anticoagulation around delivery. Vaginal delivery is preferred in the absence of obstetric indications for Caesarean delivery.
Post-partum	Contraception	Safe and effective contraception should be offered: progesterone-only pill, intrauterine device, progesterone implant.
	Breast-feeding	Breast-feeding should be encouraged and supported. Prescribed medication should be compatible with lactation (see https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).
	On–going renal replacement therapy	Dialysis regimens should accommodate breastfeeding. The decision to (re)activate on transplant lists should be collaborative. Consider: •transplant immunosuppression may not be compatible with lactation •balance between neonatal/family commitments and the required time in hospital should a transplant become available.

There is now emerging evidence to support the use of angiogenic (placental growth factor, PlGF) and antiangiogenic (soluble fms-like tyrosine kinase, sFlt-1) biomarkers in the prediction and diagnosis of pre-eclampsia. Low circulating concentrations of PlGF, high concentrations of sFlt-1, and an elevated ratio of sFlt-1:PlGF have been shown to be useful tools for the prediction of pre-eclampsia [50] and the need for delivery [51] in the general obstetric population. Similar biomarker profiles are reported in women with chronic hypertension and CKD [48], and in a case report of a woman receiving dialysis in pregnancy [52]. Rolfo et al. was able to demonstrate distinction of CKD from pre-eclampsia using the ratio of s-Flt-1:PlGF, although superimposed pre-eclampsia was not examined [53]. The negative predictive value of a sFlt-1:PlGF ratio >85 in 29 women with early stage CKD (creatinine <118 μmol/L) was found to be 98% [48], which suggests promising clinical utility for the exclusion of pre-eclampsia, particularly in women presenting with non-specific symptoms, although validation in women with advanced CKD is required.

Commencing haemodialysis in pregnancy

Published literature from 1985 to 2007 shows that women with a pre-pregnancy creatinine >180 μmol/L have a 70% chance of a decline in renal function during pregnancy [54]. Contemporary cohorts show the risk of progression to dialysis in pregnancy is 20–50% for women with a pre-pregnancy eGFR <30 ml/min/1.73 m^2 [21,55]. In the event of such a decline in renal function in pregnancy, the clinical dilemma of when to start dialysis in pregnancy remains.

Indications for commencement of dialysis in the non-pregnant population include symptomatic uraemia, evidence of protein-energy wasting, and the inability to safely manage metabolic abnormalities and/or volume overload with medical therapy [34]. However, in the context of pregnancy, the fetotoxicity of urea is likely to precede any maternal indications for dialysis, although the absolute level of urea at which the provision of dialysis improves pregnancy outcome remains unknown. Studies that have examined the level of urea at which fetal harm occurs are largely historical. In 1963, there were no surviving infants in a cohort of women with urea >21.4 mmol/L [56] and in 1968, a maternal urea >17.9 mmol/L was associated with 50% infant survival [57], although such outcomes also reflect standards of obstetric, renal and neonatal care from 50 years ago. Current practice remains variable; from automatic commencement of dialysis when urea is > 17 mmol/L [58], to the *consideration* of dialysis only for women with progressive loss of renal function and a urea consistently >20 mmol/L [16].

Residual renal function is hypothesised to contribute to the better outcomes seen in women commencing dialysis during pregnancy, compared to women established on dialysis prior to pregnancy [59]. As residual function confers some filtration capacity, intensification of dialysis may not show the same benefit for women initiating dialysis in pregnancy as it does for women established on haemodialysis prior to pregnancy who have no significant residual function. Meta-analysis data demonstrating improved outcomes with intensification of dialysis do not include women starting dialysis after 20 weeks gestation so should not be generalised [7]. In a study of intensive dialysis in pregnancy, a subgroup analysis of women commencing haemodialysis after conception showed no significant difference in gestational age at delivery between those receiving 33 ± 6 hours/week (n = 4) compared to 15±4 h/week (n = 13) [30]. In the absence of benefit to pregnancy outcome, it is therefore important to consider the potential disadvantages of intensive dialysis in pregnancy including treatment burden and an accelerated decline in residual renal function [34]. Despite increasing recognition that dialysis in pregnancy should be adjusted to residual renal function [16], validated methods for the assessment of residual renal function in pregnancy do not exist.

Whether the initiation and prescription of dialysis in pregnancy based on serum urea concentration or alternative measures of urinary clearance can optimise pregnancy outcome remains unknown. In the absence of better evidence, current expert consensus advises that commencement of dialysis in pregnancy is informed by urea concentration in combination with the trajectory of renal function decline, fluid balance, blood pressure control and gestation, in combination with the views and preferences of the pregnant woman. The risks of commencing dialysis in pregnancy should be weighed against those of preterm delivery, especially after 34 weeks gestation when there is a recognised reduction in risk to the neonate [37].

Peritoneal dialysis and pregnancy

Incidence of pregnancy is lower for women on peritoneal dialysis compared to haemodialysis (see: Fertility and dialysis). Although successful pregnancies on peritoneal dialysis are described, less than 100 reported cases of peritoneal dialysis in pregnancy have been reported worldwide [60]. Batarse et al. (2015) examined outcomes in 47 pregnant women treated with peritoneal dialysis in pregnancy. Overall infant survival was 77%, at a mean gestational age of 33 weeks, with a mean birth weight of 1755 g [61]. Jefferys et al. published a series of 5 patients with early-start peritoneal dialysis in pregnancy (mean urea concentration of 14.6 mmol/L). Median gestation at delivery was 35 weeks (range 25–38 weeks), and complications of peritoneal dialysis were frequent; exit site infection, catheter displacement and peritonitis [62]. Systematic review data reveals that, despite comparable rates of preterm delivery, peritoneal dialysis is associated with a higher rate of small-for-gestational-age infants

(67%) compared to haemodialysis (31%) [7]. Although cohort size and publication bias may inform these data, this finding has led to the hypothesis that placentation could be adversely affected by the mechanics of peritoneal dialysis.

Peritoneal dialysis offers potential benefits for pregnancy including continuous ultrafiltration, avoidance of haemodynamic fluctuation, and no requirement for anticoagulation at the time of delivery. However, progressive distension of the uterus may necessitate reduced dialysate volumes and affect catheter position leading to concern about the capacity to intensify dialysis requirements in pregnancy. HD therefore remains the modality of choice in pregnancy, with most experts advocating a switch from PD to HD in pregnancy in order to facilitate controlled intensification of dialysis [19], although the supplementation of peritoneal dialysis with intermittent haemodialysis in order to augment clearance has been described [63].

The choice of dialysis modality in pregnancy should be informed by availability, local expertise, current and anticipated dialysis efficiency, residual renal function, gestation, infection risk, and patient choice.

Summary

Pregnancy rates in women on dialysis have increased and the effects of end-stage renal disease on fertility may be reversed by intensified dialysis. Contraceptive and pre-pregnancy counselling are therefore required for women on dialysis. Lower risk reproductive options should be considered, including transplantation. An experienced, multidisciplinary team should manage all women on dialysis in pregnancy.

There is an association between increased dialysis time and improved neonatal outcomes for women on dialysis prior to pregnancy. Intensification of dialysis can be achieved by an increase in dialysis time and the use of pre-dialysis urea targets. Current recommendations include haemodialysis for >36 h/week [37,39] and/or a target pre-dialysis urea <12.5 mmol/L [23].

There is an increased risk of pre-eclampsia in women on dialysis, the development of which is a key determinant of pregnancy outcome. However, diagnosis of superimposed pre-eclampsia is complex with no diagnostic criteria. There is emerging evidence that circulating concentrations of PlGF and sFlt-1 have diagnostic utility in pregnancy, and in women with CKD, but validation in dialysis cohorts is required.

For women with advanced CKD, dialysis in pregnancy may be commenced due to the fetotoxicity of urea, rather than for maternal indications. Residual renal function contributes to clearance and evidence that dialysis should be intensified in the same way for women newly commenced on dialysis in pregnancy as for women established on dialysis prior to pregnancy does not exist. The concentration of urea at which it is beneficial to provide dialysis in pregnancy remains unknown but a level >15 mmol/L should initiate a conversation in all cases.

Limited published data on peritoneal dialysis suggest there may be modality-specific adverse effects on fertility and fetal growth, and intensification of dialysis may be harder to achieve. PD is therefore considered an inferior choice if HD is feasible and acceptable to women.

Research agenda

- Standardisation of data collection from dialysis cohorts and the establishment of multicentre registries to allow prospective, large cohort analysis of factors contributing to pregnancy outcomes in women on dialysis including maternal urea concentration, residual renal function, dialysis modality, renal disease aetiology, blood pressure, maternal haemoglobin and cervical length.
- The validation of angiogenic (PlGF) and antiangiogenic (sFlt-1) biomarkers in the prediction and diagnosis of pre-eclampsia in women on dialysis.
- Qualitative evaluation of methods used to communicate risk in pregnancy in order to increase the understanding of risk and facilitate shared decision-making in reproductive health.

Conflicts of interest

None.

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