Nephrol Dial Transplant (2016) 31: 1915–1934
doi: 10.1093/ndt/gfv395
Advance Access publication 27 November 2015

ndt
Nephrology Dialysis Transplantation

Original Articles

Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes

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ABSTRACT

Background. Advances have been made in the management of pregnancies in women receiving dialysis; however, single-centre studies and small numbers of cases have so far precluded a clear definition of the relationship between dialysis schedules and pregnancy outcomes. The aim of the present systematic review was to analyse the relationship between dialysis schedule and pregnancy outcomes in pregnancies in chronic dialysis in the new millennium.

Methods. Medline–PubMed, Embase and the Cochrane library were searched (1 January 2000–31 December 2014: MESH, Emtree, free terms on pregnancy and dialysis). A separate analysis was performed for case series (more than five cases) and case reports. Meta-regression was performed in case series dealing with the larger subset of haemodialysis (HD) patients; case reports were analysed separately [according to peritoneal dialysis (PD) versus HD; conception before or during dialysis].

Results. We obtained 190 full texts and 25 congress abstracts from 2048 references. We selected 101 full papers and 25 abstracts (36 series; 90 case reports), for a total of 681 pregnancies in 647 patients. In the case series (574 pregnancies in 543 patients), preterm delivery was extremely frequent (83%). Meta-regression analysis showed a relationship between hours of dialysis per week in HD and preterm delivery, and was significant for preterm deliveries (<37 gestational weeks: $P = 0.044$; $r^2 = 0.22$) and for small for gestational age (SGA) ($P = 0.017$; $r^2 = 0.54$). SGA was closely associated with the number of dialysis sessions per week ($P = 0.003$; $r^2 = 0.84$). Case report analysis suggests a lower incidence of SGA on HD versus PD (31 versus 66.7%; $P = 0.015$). No evidence of an increased risk of congenital abnormality was found in the retrieved papers.

Conclusions. Data on pregnancy on dialysis are heterogeneous but rapidly accumulating; the main determinant of outcomes on HD is the dialysis schedule. The differences between PD and HD should be further analysed.

Keywords: haemodialysis, maternal–foetal outcomes, peritoneal dialysis, pregnancy, preterm delivery

INTRODUCTION

Dialysis is unique in the field of medicine as it represents the only possibility to substitute the lost function of a complex organ for the rest of one's life [1, 2].

In the era of transplantation, the technical miracle of dialysis has sometimes been overlooked due to the obvious advantages of a 'natural' substitution of kidney function via a functioning kidney graft: pregnancy outcomes have historically been considerably better in women with renal transplants, a population

in which fertility has been at least partly restored. Indeed, even though one of the first papers reporting a successful outcome of pregnancy in a 35-year-old woman on twice weekly dialysis for 2 years dates back to 1971 [3], in the 1980s and 1990s, the idea that transplantation would solved the clinical problems of all young dialysis patients led to greater attention being given to pregnancy after kidney transplantation, while the issue of pregnancy on dialysis was relegated to the role of clinical exception [3, 4].

However, both the shortage of organs and the great advances in chronic dialysis are creating a different scenario: the limited availability of kidneys for transplantation may lead to prolonged waiting times, often too long to be compatible with pregnancy in a woman with end-stage kidney disease who is already in her late 30s.

It must also be kept in mind that the guidelines suggest waiting at least 1 year after transplantation and then starting pregnancy with stable, and whenever possible, normal kidney function, which is not always attainable, and above all remains unpredictable [5–7].

The advances in dialysis treatments, together with increasing experience with long-hour, quotidian haemodialysis (HD) and the diffusion of dialysis in countries where the local culture strongly supports large families has led to a growing number of case series of pregnancy on dialysis in the new millennium [8–43].

A previous systematic review on pregnancy on dialysis regarding the period between 2000 and 2008 collected series of at least 5 cases and included 90 pregnancies [4]. Only 6 years later, for the present analysis, which covers the period between 2000 and 2014, we collected >600 cases. This may be a reflection of the dramatic increase in the interest towards dialysis and pregnancy, enhanced by the better neonatal outcomes and by the different approach towards 'high-risk' pregnancies; a further role may have been played by fertility treatments and by publication bias favouring reporting the more frequent positive results. This remarkable increase in available data allowed us to take a meta-analytic approach to identify which dialysis policies correlate with the best outcomes.

The aim of this study was to systematically review the literature on pregnancy on dialysis in the new millennium in an effort to clarify the major risks, outcomes and treatment suggestions and to identify optimal regimes associated with the best pregnancy outcomes, with minimal adverse consequences for mother and neonate.

The results may also be of interest for their application in the advanced phases of chronic kidney diseases or in patients with a failing kidney graft who become pregnant, since the decision on dialysis start is also crucial in these cases.

MATERIALS AND METHODS

Study design

The analysis was performed separately for case series, defined as those including at least five cases, and case reports, regarding one to four cases.

The PICOS criteria were applied as follows: P: patients on chronic dialysis in pregnancy; I: interventions: dialysis schedules; C: control groups were included when present in the papers; O: maternal outcomes; foetal outcomes; S: side effects.

Owing to the ethical constraints, no randomized studies were available and only few studies compared different dialysis schedules; therefore, a meta-regression design, regardless of a control group, was chosen to combine the data. Owing to the higher prevalence of HD patients, and to the wide dispersion of information on peritoneal dialysis (PD) schedules, the meta-regression was limited to HD patients.

The analysis of case reports was performed by entering each case report as an individual patient into a dedicated database; case reports were subdivided into: HD, conception before dialysis start; HD, conception on chronic dialysis; PD, all cases.

Search strategy

The search included papers published between 1 January 2000 and 31 December 2014 and was built on Medline–PubMed, Embase and the Cochrane database. The following terms were used as MESH, Emtree terms or free terms: pregnancy or pregnant or gestation and dialysis, or HD or renal replacement therapy.

F.M. and G.B.P. independently performed the search, screened abstracts and titles and selected the papers in duplicate. Complex cases were discussed, with the supervision of E.V.

The selection criteria included: pregnancy in chronic dialysis patients; only patients who started dialysis within the first 20 weeks of gestations were included; in an attempt to reduce reporting biases, in case reports (often reporting only on the successful outcomes) and in series (in retrospective studies, early losses may be missed), pregnancy interruption before the 24th gestational week ('abortions') was also excluded [44].

Duplicate publications

When several papers dealt with the same case series, we chose to analyse the most recent and/or larger series. In case of partial duplicates, or incomplete overlap, we chose the paper dealing with the selected outcomes and covariates; if data were available in two or more papers, the most recent and/or larger one was selected.

In case of papers that were not available as full texts, we made every effort to obtain the data from the authors; otherwise, we employed the abstract as the source of data.

Data extraction and main definitions

The following data were extracted: baseline: title, author, objective, year, journal, period of study, prospective, retrospective or registry study, country, type of study, number of cases, control group, maternal age, subcategories, parity, type of dialysis, dialysis schedules, support treatment.

Maternal and foetal outcomes included were hypertension, gestational age at delivery, birth weight, preterm delivery (<37 completed gestational weeks); early preterm delivery (<34 completed gestational weeks); very early preterm delivery (<28 completed gestational weeks); birth weight; gestational week; small for gestational age (SGA) baby (SGA: birth weight <10 percentile according to the international standards—IneS charts) [44, 45], malformations, stillbirth/neonatal death, SGA, admission to neonatal intensive care unit, other neonatal complications,

and maternal and foetal follow-up. All available data on long-term results were also extracted.

Since the definitions of pregnancy termination, stillbirth, abortion and neonatal death were non-univocal, we tried to reclassify the data according to the following definitions: abortions were considered as births occurring before 24 gestational weeks; after this time, we employed the term 'intrauterine death' for stillborn babies. Conversely, we employed the term 'neonatal death' for children who were live-born but who died within the first month of life [44–46]. Since these distinctions were not always possible, we analysed the data regarding live-born babies separately.

Statistical analysis: case series

Descriptive analysis was performed by estimating proportions with 95% confidence intervals (CIs) or means and standard deviations.

Significance was tested using χ^2 or Fisher's exact test when necessary for proportions, and parametric or non-parametric tests for continuous variables, according to their distribution.

Meta-analysis was performed using Metanalyst software. We obtained a pooled proportion of events using the random-effect model of maximum likelihood. The choice of the random-effect model was due to the heterogeneity, estimated by the I^2 statistic, among studies. The pooled proportion of events is a mean of the measurements of every single study, weighted by the number of cases generated by the study itself; 95% CIs were estimated in the same way [47]. Despite the use of a random-effect model, a certain level of heterogeneity persists (I^2 statistic >50%).

Subgroup analysis was performed to test the effects of hours of dialysis and the number of sessions of dialysis on the outcomes.

Meta-regression was performed using the same software (Metanalyst) to test the effect of the covariates on the outcome measure; the effect is weighted, and the more precise studies have greater influence in the analysis. The strength of the association is summarized by R^2 [48, 49].

The following outcomes were considered: preterm delivery (<37 completed gestational weeks); early preterm delivery (<34 weeks); very early preterm delivery (<28 weeks) and SGA baby (SGA: birth weight <10th percentile according to IneS charts) [44, 45].

The following covariates were tested: minimum number of dialysis sessions per week, continuous (meta-regression) or dichotomized at six sessions per week; number of hours of HD per week, continuous or dichotomized at 20 h per week; since the hours per week were reported differently (median, mean and most common schedule), whenever it was not possible to recalculate the data, we entered the measurement indicated in the paper into the model.

Owing to the heterogeneity and inconsistency of the definitions of abortions, stillbirths and neonatal deaths, we focused on live births for the meta-analysis of preterm delivery; both live births and stillbirths were included with regard to SGA.

Statistical analysis: case reports

The single cases were entered into a dedicated database, gathering all the items that were previously described for case series.

The cases were subdivided into the following subgroups: HD: conception before dialysis treatment; HD: conception while on dialysis; PD, all cases.

Descriptive analysis was performed by estimating proportions or means and standard deviation. Significance was tested using χ^2 or Fisher's test when necessary for proportions and parametric or non-parametric tests for continuous variables, depending on their distribution.

RESULTS

Retrieving the evidence and summary data

In our search, we retrieved and screened 2048 titles and abstracts; 190 papers and 25 congress abstracts were assessed for further eligibility. This resulted in a final selection of 36 case series (29 full texts and 7 congress abstracts; HD 28, PD 2, HD and PD 6) and 90 case reports (72 full texts and 18 abstracts HD 77, PD 12, HD and PD 1) with data on maternal and/or foetal outcomes in women on dialysis (Figure 1). Only one article, which, according to its title, was a single-case report, could not be retrieved [50]. Two congress abstracts were excluded since they did not supply any information on pregnancy outcomes [51, 52].

Overall, after excluding duplicates and partially duplicate cases and series, we were left with 681 pregnancies in 647 patients; 616 pregnancies were reported on HD and 65 on PD.

Duplicate and overlapping papers

Shahir [13] and Jesudauson [12] reported different patient selections and outcomes with partial overlap; the largest, most recent series was selected [13].

The three reports by Bernasconi *et al.* regard progressive updates of the same series [17–19]; the most recent report was included in the meta-analysis [17].

The study by Barua *et al.* [11] describes seven patients, four of whom were included in the larger more recent series of Hladunewich *et al.* [10]; the latter study alone was included in the meta-analysis. Different outcomes were analysed in the same patients in the studies by Bamberg *et al.* [33] and Haase *et al.* [34, 35]: all the outcomes were gathered, and the cases were counted only once. The same was applied to the letter and paper by Moranne *et al.* [39, 40].

Case series: overview

After excluding duplicate and partially duplicate publications, we reviewed the selected case series, which included data on 523 pregnancies on HD and 51 on PD (overall 574 pregnancies in 543 women). As expected given the nature of the topic, no randomized trials were found, and all the studies were observational (1 prospective, 24 retrospective, 3 registry and 2 non-specified; Tables 1–5). The geographical origins were extremely widespread: the studies were heterogeneous with regard to the study period and number of cases: on HD, 78 pregnancies came from Europe, 103 from North America, 91 from Asia, 69 from Australia, 143 from South America and 39 from Africa. Most of the PD cases were reported from

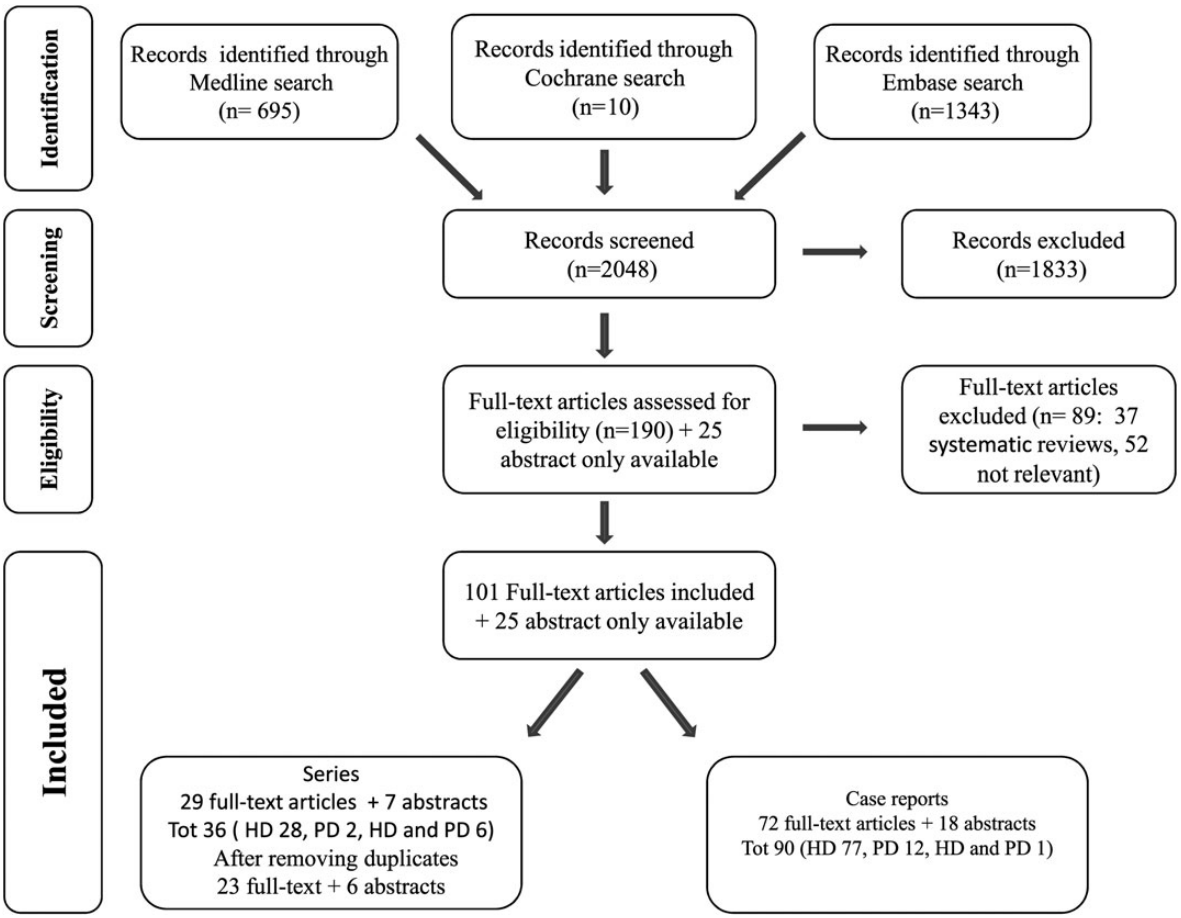

FIGURE 1: The flow chart of the systematic review: paper retrieval and selection.

North America (27 cases), 3 from Europe, 4 from Asia, 13 from Australia and 4 from South America.

The study period was highly heterogeneous (1–32 years of observation), as was the number of reported cases (5–70 pregnancies; Table 1).

Case series: follow-up policies and main therapies

Detailed information on policies was available in 12 papers (Table 2) and data on dialysis schedules were available in 22 papers on HD and in 3 papers on PD (Table 3).

Overall, the follow-up policy may be summarized as an intensification of the usual blood and clinical examinations of dialysis patients and by the application of a strict obstetrical control policy. However, these policies vary markedly, presumably as a reflection of the experience and of the differences in availability of specialized facilities, as well as of the rapid evolution of maternal–foetal care worldwide. As highlighted by some of the most informative and recent papers, cooperation among experts is one of the keys for success [10, 17, 22] (Table 2).

Drug therapy is reported in 19 papers; anti-hypertensives, erythropoietin, iron and vitamins (group B vitamins, vitamin D and folate) are the most often cited therapies. Furthermore, due to the difficult management of anaemia in pregnant dialysis patients, blood transfusions are cited in most of the series (Table 3).

Case series: dialysis schedules

Dialysis schedules are only consistently described for HD, while the different descriptions in the three papers reporting on PD prevent pooling of the data, in keeping with the continuous adjustments of the PD schedule throughout pregnancy (Table 3).

HD schedules follow the common rule of increasing frequency and, in most cases, duration in pregnancy. The most common frequency is five to six times per week, and the median dialysis time per session is 4 h. Generally speaking, over time there is a trend towards increasing time on dialysis; however, the reports regard different time periods, and the publication date only partially reflects the changes that have occurred over time. The most frequently reported dialysis schedule is 3.5–4 h, with five to six sessions per week.

On the basis of the observed pattern of dialysis frequency and duration, we empirically chose two cut points (at least six dialysis sessions versus up to five dialysis sessions per week and more or less than 20 h of dialysis per week; Table 3 and Figure 2).

Case series: maternal and foetal outcomes

The main maternal and foetal outcomes are reported in Tables 4 and 5.

Prematurity was extremely frequent in most series, and the median gestational age is in the range of early preterm delivery (33 weeks, minimum 26 maximum 39 weeks). The reports are

Table 1. Main characteristics of the case series (duplicate or partially overlapping papers in italics)

Author, year [ref.]	Years	Country	Study	Objective, as stated in the study	Cases	Dialysis	
						HD	PD
Panaye, 2014 [8]	1985–2013	France	Ret	To determine pregnancy outcome in HD patients and to identify factors influencing maternal and foetal prognosis	26 P	26	0
Ståhl, 2014 [9]	NR	Sweden	Ret	NR	5 P	5	0
Hladunewich, 2014 [10]	2000–13	Canada	Reg	To compare pregnancy outcomes from 22 pregnancies on nightly long dialysis with 70 pregnancies in the American Registry for Pregnancy in Dialysis	22 P, 17 W	22	0
	1990–2011	USA			70 P	70	0
Barua, 2008[a] [11]	*2001–06*	*Canada*	*Pro*	*To describe maternal and foetal outcomes as well as changes in clinical and biochemical indices before and after conception*	*7 P, 5 W*	*7*	*0*
Jesudason, 2014 [12]	2001–11	Australia	Reg	To describe a large series of pregnancies in women undergoing long-term dialysis comparing women who had conceived before and after starting dialysis	77 P, 73 W	69	8
Shahir, 2013[b] [13]	*1966–2008*	*Australia*	*Reg*	*To conduct a study examining pregnancy outcomes in dialysed women using the ANZDATA Registry*	*49 P*	*41*	*8*
Piccoli, 2014 [14]	2000–12	Italy	Ret	To assess the incidence of live births from mothers on chronic dialysis compared with the overall population and kidney transplant patients	23 P	20	3
Espinoza, 2013 [15]	1985–2012	Chile	Ret	To repost the experience in six dialysis patients who became pregnant	6 P	6	0
Zanlorenci, 2013* [16]	1999–2007	Brazil	Ret	To study the obstetrical and perinatal outcomes of 30 pregnancies in 27 patients on dialysis	30 P, 27 W	30	0
Bernasconi, 2013* [17]	NR	Argentina	Ret	To report the experience in a multidisciplinary team for pregnant women suffering from ESRD in a Public Hospital	37 P, 37 W	37	0
Bernasconi, 2012[c]* [18]	*2000–12*	*Argentina*	*Ret*	*To review treatment and outcome on intensive HD (>20 h/week) and to perform a combined analysis to find out when pregnancy is advisable in this population*	*31 P, 30 W*	*31*	*0*
Bernasconi, 2007[c] [19]	*1994–2006*	*Argentina*	*Ret*	*To determine if there were significant differences when comparing HD (>20 h/week) and conventional schemes.*	*27 P, 27 W*	*27*	*0*
Abou-Jaoude, 2012 [20]	1989–2009	France	Ret	To evaluate mid-term renal prognosis in children of mothers undergoing HD during pregnancy	10 P, 7 W	10	0
Macias, 2012* [21]	2002–11	Mexico	Ret	To describe the course and perinatal outcomes of women who initiated PD during the second trimester of pregnancy	27 W	0	27
Hadj Sadek, 2011 [22]	2000–10	Morocco	Ret	To report the experience in the management of pregnancies occurring in HD patients, and to clarify the factors of good prognosis	11 P, 8 W	11	0
Sulaiman, 2011* [23]	NR	USA	NR	To report a single-centre experience of five patients requiring dialysis during pregnancy	5 P	5	0
Bahadi, 2010 [24]	1999–2007	Morocco	Ret	NR (retrospective analysis of clinical charts)	9 P	9	0
Luders, 2010 [25]	1988–2008	Brazil	Ret	To summarize maternal and foetal outcomes and prenatal management of 52 pregnancies in women on HD at a single institution	52 P, 52 W	52	0
Sato, 2010[d] [26]	1996–2006	Brazil	Ret	To report on the treatment and outcome of pregnancy in 29 women with chronic kidney disease	22 P	18	4
Vázquez-Rodríguez, 2010 [27]	1–12/2008	Mexico	Ret	To compare perinatal complications in patients already on dialysis and who started dialysis in pregnancy	6 P	6	0
Boubaker, 2010* [28]	1975–2007	Tunisia	Ret	To investigate the pregnancy outcome in patients on chronic HD over the past 30 years in the department	7 P, 6 W	7	0
Asamiya, 2009 [29]	1986–2007	Japan	Ret	To study the clinical characteristics and the outcomes of 28 pregnant women receiving HD in a single centre	28 P	28	0
Unuigbe, 2009* [30]	NR	Saudi Arabia	NR	To assess the maternal and perinatal outcome among patients with chronic renal failure and renal transplant recipients	9 P	9	0
Chou, 2008 [31]	1990–2006	Taiwan	Ret	To investigate the pregnancy outcome in patients on chronic dialysis over the past 15 years in a single centre	10 P	7	3
Jefferys, 2008 [32]	1998–2008	Australia	Ret	To present the experience over 10 years of two teaching hospitals with PD for significant renal impairment in pregnancy	5 P	0	5
Bamberg, 2007 [33]	2000–04	Germany	Ret	To evaluate the effect of foetal surveillance by Doppler ultrasound and foetal non-stress test on outcome of pregnancy on intensified HDF	5 P	5	0
Haase, 2005, 2006[e] [34, 35]	*2000–04*	*Germany*	*Pro*	*To report the multidisciplinary management of five pregnant dialysis patients*	*5 P*	*5*	*0*
Tan, 2006 [36]	1995–2004	Singapore	Ret	To report obstetric outcomes in women undergoing chronic renal dialysis	11 P, 7 W	10	1
Malik, 2005 [37]	1992–2003	Saudi Arabia	Pro	To report the frequency and outcome of pregnancies in women on dialysis from a referral centre	12 P, 9 W	12	0
Eroğlu, 2004 [38]	2000–02	Turkey	Ret	To review the treatment and outcome of seven pregnancies on HD	7 P	7	0
Moranne, 2004, 2006[f] [39, 40]	1995–2001	France	Ret	To report on seven pregnancies on dialysis. To discuss the collaborative approaches by obstetrician, paediatrician and nephrologist	7 P, 6W	7	0
Bahloul, 2003 [41]	1990–96	Tunisia	Ret	To assess the frequency of pregnancy in women on HD and the complications that may occur in mother and foetus	12 P, 11 W	12	0

Continued

Table 1. Continued

Author, year [ref.]	Years	Country	Study	Objective, as stated in the study	Cases	Dialysis	
						HD	PD
Chao, 2002 [42]	1990–2000	Taiwan	Ret	To describe the pregnancy outcome in a series of patients undergoing long-term HD	18 P, 15 W	18	0
Luciani, 2002 [43]	1988–98	Italy	Ret	To review the patients on HD to identify the factors that may affect the course of the pregnancy and the foetal outcome	5 P	5	0

ESRD, end-stage renal disease; Ret, retrospective; Reg, registry; Pro, prospective; NR, not reported; P, pregnancy; W, woman; HD, haemodialysis; PD, peritoneal dialysis; HDF, haemodiafiltration.
*Abstract only.
[d]Sato: 29 pregnancies, 22 on dialysis: dialysis and pre-dialysis data are presented together.
Duplicate publications:
[a]Barua 2008: partial duplicate four of seven cases included in Hladunewich 2014. Not included in meta-analysis.
[b]Shahir 2013 and Jedauson 2014: overlapping population (ANZDATA 1996–2008 and 2001–11) the most recent and largest series was considered for the final count.
[c]Bernasconi 2007, 2012, 2013: partial overlap of data. The largest and most recent series (2013) was included in the meta-analysis.
[e]Haase 2005 and Haase 2006 and Bamberg 2007: same series, different outcomes and design, information from the three papers, included only once in the meta-analysis.
[f]Moranne 2004 and 2006: same series, different outcomes and design, information from both papers, included only once in the meta-analysis.

Table 2. Case series: maternal and foetal control policies in the papers reporting them

Author [ref.]	Dial	Control policies: foetal monitoring	Other control policies
Hladunewich [10]	HD	11–14 w: nuchal translucency 15–20 w: maternal serum screen or quadruple test 18–20 w: level II ultrasound (to exclude foetal anomalies and measure cervical length) 22–24 w: placental ultrasound, umbilical artery Doppler From 26 w: ultrasounds every 2 weeks, weekly near term or in case of pregnancy complications. Induction of labour before 39 w to coordinate HD care	Obstetrician specialized in high-risk pregnancies supported by a designated nephrologist Biochemical tests at least monthly
Bernasconi [17]	HD	Foetal well being closely monitored throughout pregnancy; ultrasound performed from the beginning, and foetal placental Doppler from week 12	Multidisciplinary team (obstetrician and nephrologist)
Hadj Sadek [22]	HD	12–14 w; 22–24 w; 32–34 w: foetal ultrasound and uterine length measurement. In case of IUGR: tococardiography, umbilical artery and cerebral artery Doppler	Multidisciplinary team (obstetrician and nephrologist). Evaluation of dry weight, signs of PE, blood count, liver indexes, uric acid. Electrolytes and haemoglobin pre-post dialysis
Bahadi [24]	HD	Uterine ultrasound every week	Close obstetric observation. Monitoring of weight gain
Luders [25]	HD	Second- and third-trimester: Doppler studies every 15–30 days in outpatients, then every week after hospitalization. Prenatal visits: every month up to 20 weeks and twice a month or every week thereafter	Laboratory tests for PE twice a month (Plts, liver enzymes, haemolysis and proteinuria)
Chou [31]	HD PD	NR (retrospective analysis of clinical charts)	Blood biochemistry and haemoglobulin pre-post dialysis. Dry weight recorded
Bamberg and Haase [33–35]	HD	Weekly sonographic measurement of cervical length. After 25 w: cardiotocography (twice a week to daily), weekly uterine-umbilical Doppler. After dialysis, uterine contraction monitoring and pharmacological tocolysis	BP every 15 min during dialysis Targets: metabolic parameters to physiological levels. Double pool K_t/V repeatedly calculated
Tan [36]	HD PD	Antenatal visits every 2 w (obstetricians and nephrologists). Serial foetal biometric measurements, biophysical profile, foetal Doppler assessment. Mode and timing of delivery based on obstetric indications. Check for dialysis-induced contractions and tocolysis if necessary	Monitoring of fluid status, BP, maternal weight, biochemical test. Targets: BP 140/90 mmHg, pH and electrolytes near normal, BUN 20 mmol/L
Malik [37]	HD	Obstetric evaluation every 2 w	NR
Eroğlu [38]	HD	Every 2–4 w: ultrasonography. After 24 w: cardiotocography twice weekly and Doppler flow measurements weekly. After dialysis: uterine contraction monitoring	Multidisciplinary team (obstetrician and nephrologist)
Chao [42]	HD	NR (retrospective analysis of clinical charts)	Counselling on risks, dialysis treatment, prenatal surveillance
Luciani [43]	HD	Every 2 w: foetal ultrasonography. Foetal heart rate after each HD session. Daily measuring of maternal BP	Multidisciplinary team (obstetrician and nephrologist)

Duplicates not included; the most relevant paper is cited; when relevant information was available in a different paper on the same series this was added to the table.
Dial, dialysis; HD, haemodialysis; PD, peritoneal dialysis; w, weeks; BP, blood pressure; BUN, blood urea nitrogen; IUGR, intrauterine growth restriction; NR, not reported; PE, pre-eclampsia; Plts, platelets.

highly heterogeneous and it is often difficult to extract data regarding abortions (defined as delivery before the viability period), stillbirths and neonatal deaths (Table 4).

The differences in design prevent precise quantification of prenatal and neonatal deaths. Within these limits, the prevalence of perinatal deaths is high (63 deaths, considering

Table 3. Case series: dialysis schedules in the papers reporting them

Author [ref.]	Dial	Dialysis schedule	EPO, iron and vitamins, heparin	Other main drugs	Weight gain, diet
Panaye [8]	HD	6 days/w 17.7 ± 4 h/w	NR	NR	NR
Ståhl [9]	HD	Individualized 6 days/w 2.5–4 h	EPO; heparin; iron; vit B12; vit D; folic acid; Zn	$CaCO_3$; ASA; antihypertensive; transfusions	Overall weight gain range 4–22 kg
Hladunewich [10]	HD CAN	6–8 h 6–7 days/w after conception	EPO, iron (i.v.): target Hb 10–11 g/dL	Antihypertensive	No dietary restrictions; phosphate supplementation
	HD US	17 ± 5 h/week 4 h × 5–6 days/w	NR	NR	NR
Piccoli [14]	HD PD	HD: up to 6 h 7 days/w; most common: 4 h 6 days/w	NR	NR	NR
Espinoza [15]	HD	19.5 ± 2.7 hours/w	EPO	Transfusions Antihypertensive	Weight increase: 500 g/2 weeks
Zanlorenci [16]	HD	NR	EPO	Antihypertensive	NR
Bernasconi [17]	HD	From 3 days/w to 5–6 days/w	EPO, vit B, heparin	Antihypertensive $CaCO_3$	NR
Abou-Jaoude [20]	HD	Median 18 h/w (12–30)	NR	NR	NR
Macias [21]	PD	63.3 L/week	NR	NR	NR
Hadj Sadek [22]	HD	4 h 3 days/w or 4 h 4 days/w	EPO, heparin, oral iron	Transfusions	Unrestricted diet. Weight gain 300 g/w second trimester; 300–500 g/w third trimester
Sulaiman [23]	HD	Mean 23.2 ± 1.8 h/w	EPO	NR	NR
Bahadi [24]	HD	4–6 days; duration to 6 h. Average 18 h/w	EPO, oral iron	Transfusions Antihypertensive	Weight gain 0.3–0.5 kg/w in second—third trimester
Luders [25]	HD	1988–99: 3 h 4–6 days/w; 2000–08: 6 days/w, 1.5–3 h Mean 15 (9–21) h/w	EPO, aspirin $CaCO_3$	Transfusions	NR
Sato [26]	HD PD	HD: 12–20 h/week	NR	Transfusions	NR
Vázquez-Rodríguez [27]	HD	HD before pregnancy: 4 h × 3 days/w	Oral iron, vit B, folic acid	Transfusions	NR
Asamiya [29]	HD	First trimester: 12.7 ± 2.5 h/w; second: 15.9 ± 3.1 h/w; third: 18.4 ± 2.6 h/w	EPO, iron	Transfusions Antihypertensive	Weight gain: 127.1 ± 167.4 g/w second trimester; 193.6 ± 111.0 g/w third trimester
Chou [31]	HD PD	HD: 15–27 h/w	EPO, oral iron	Transfusions Antihypertensive	Weight gain in pregnancy 9.7 ± 2.7 kg
Jefferys [32]	PD	5.4–7.5 L. Cycler: 10 L in 9 h plus 1 daytime exchange	EPO, oral iron, vit D, $CaCO_3$	Antihypertensive	NR
Bamberg [33]	HD	6 days/w (28.6 ± 6.3 h/w; 4.6 ± 0.9 h/day) >24 h/w	EPO, iron, trace elements, vit D, vit B, folate	Transfusions, Mg celestan in preterm delivery	Weight gain 500 g/10 days if appropriate; 100 g protein, 3000 kcal/day
Tan [36]	HD PD	HD: 6 days/w; 3 h; PD: 6 exchanges/day	EPO, vitamins, folate	ASA, antihypertensive	NR
Malik [37]	HD	4–6 days/w	EPO	NR	NR
Eroğlu [38]	HD	4–6 days/w, 4 h	EPO	Antihypertensive	Weight gain: 300 g/week second trimester; 300–350 g/week third trimester
Moranne [39]	HD	3 days/w 4 h Increase in pregnancy	EPO, heparin, iron	Transfusions Antihypertensive tocolytic, steroids	NR
Chao [42]	HD	4–6 days/w 4 h	EPO, heparin	Transfusions Antihypertensive tocolytic	Dry weight gradually increased, depending on obstetric status
Luciani [43]	HD	3–6 days/w 3.5–4.5 h	EPO, heparin, iron, folate	Transfusions	Unrestricted diet. Weight gain: 1.2 ± 0.5 kg first trimester; 0.5 kg/w second–third trimester

ASA, acetylsalicylic acid; CAN, Canada; dial, dialysis; h, hours; w, weeks; Hb, haemoglobin; HD, haemodialysis; PD, peritoneal dialysis; NR, not reported; EPO, erythropoietin; US, USA; vit, vitamin.

stillbirths after 24 gestational weeks and neonatal deaths, versus 298 surviving babies in 15 papers reporting these outcomes) [10, 12, 14, 16, 21, 22, 26–29, 31, 38, 39, 42, 43].

Seven of 448 major malformations (patent ductus, 5; arm dysplasia, 1; cardiac malformation, 1) were reported in the series (PD and HD), and 2 of 107 in the case reports (patent ductus and unilateral lung agenesis), a prevalence in line with what is expected in the overall population.

It is difficult to precisely quantify the risk of maternal death; seven maternal deaths are reported in the three series that analyse long-term follow-up (up to 10 years after delivery); two deaths were reported in the first month after delivery. However,

Table 4. Case series: foetal outcomes in the papers reporting them

Author [ref.]	All cases considered					Abortions excluded (before 24 gw)		Live births only		All cases	Other
	P	Abort.	Still birth	Live birth	Neo. death	Birth weight (g)/IUGR	CS	Preterm <37 w Early <34 w Extreme <28 w	N-ICU	PE-HT	
Panaye [8]	26	NR	NR	19	NR	1951 ± 157	NR	NR	NR	NR	NR
Ståhl [9]	5	0	0	5	0	2451 (959–3630) IUGR 3 (60%)	3 (60%)	Preterm 3 (60%) Early 1 (20%)	2	HT 3 PE 2	RD: 1; jaundice: 1; cardiac malformation: 1
Hladunewich [10]	22	2	1	19	0	2118 ± 857; IUGR 3 (15%); SGA 3 (15%)	2 (10%)	36 w (IQR 32–37) Preterm 9 (50%) Early 4 (22%) Extreme 1 (6%)	7	HT 5 PE 1	Twin pregnancy: 1
	70	19	3	49	5	1748 ± 949; SGA 13 (30%)	NR	27 w IQR 21–35 Preterm 31 (74%) Early 20 (48%) Extreme 4 (10%)	NR	NR	NR
Jesudason [12]	77	29	2	46	3	1750 (1130–2417) SGA 24 (50%)	NR	Preterm 34 (74%), Early 23 (60%), Extreme 5 (13%)	NR	PE	NR
Piccoli [14]	23	0	0	24	2	1200 (590–2250); SGA 7 (33.3%)	20 singlet	Preterm 19 (90%) (singletons) Early 14 (66.6%) Extreme 3 (14%)	15	HT 14	Twin: 1; RD: 5; arm dysplasia: 1; hernia: 2; retinitis: 1; pneumonia:1; patent ductus: 2
Espinoza [15]	6	0	0	6	0	1990 (1570–2700); IUGR 1 (17%); SGA 1 (17%)	6 (100%)	Preterm 6 (100%) Early 4 (66.6%) Extreme 0	NR	HT 3	NR
Zanlorenci [16]	30	1	0	29	2	1839.3 ± 647.94 (530–3100); SGA 15 (50%)	18 (60%)	Preterm 23 (77%)	NR	HT 24	RD: 19; sepsis: 5; retinopathy: 3; enterocolitis: 1; brain hemorrh.: 1
Bernasconi [17]	37	NR	NR	37	NR	1404 ± 108	27 (70%)	Preterm 37 (100%)	22	HT 22	Twins: 3; triplets: 1; RD: 4; other: 3; retinopathy: 4; hearing disorders: 2; arrhythmia: 1; develop. delay: 3; enterocolitis: 2
Abou-Jaoude [20]	10	0	0	10	0	1735 (930–3430); <2500 g: 8 IUGR 2 (20%) SGA 2 (20%)	4 (40%)	Preterm 7 (70%) Extreme 0	7	HT 4 PE 0	Renal failure: 1; nephrolithiasis: 1; minor signs of CKD: 5
Macias [21]	27	2	4	21	6	SGA 10 (48%)	NR	Preterm 21 (100%)	NR	HT 24 PE 4	NR
Hadj Sadek [22]	11	5	1	5	0	2070 (1280–2800); IUGR 1 (17%)	1 (17%)	Preterm 4 (80%) Early 3 (60%) Extreme 0	2 (40%)	HT 5	AKI: 1; normal development: 5
Sulaiman [23]	5	0	1	4	NR	1215.4 ± 562	5 (100%)	Preterm 4 (100%) Early 3 (75%) Extreme 1 (25%) Still birth: 1 extreme	NR	HT 5	NR
Bahadi [24]	9	2	2	5	NR	2380 (1800–2900); IUGR 1 (14%)	1 (20%)	Preterm 5 (100%) Early 0 Extreme 0	NR	HT 5	NR

Luders [25]	52	0	4	50	3	1554 ± 663; SGA 24 (48%)	34 (63%)	Preterm 41 (82%)	NR	HT 35 PE 10	Twins: 2
Sato [26]	29[a]	0	6	23	0	SGA 16 (70%)	17 (74%)	Preterm 19 (82.6) <32 w: 8	NR	HT 26 PE 22	NR
Vázquez-Rodríguez [27]	6	1	0	5	2	HD pre: 1025 ± 849 HD in: 1618.3 ± 776 IUGR 1 (16.6%)	5 (100%)	3 (50%)	2 (33.3%)	HT 3 PE 3	Foetal distress: 3; RD: 2
Boubaker [28]	7	Four not specified foetal deaths	2		1570 (1000–2250); IUGR 5 (71%)	NR	Preterm 4 (57%)	NR	HT 2 (28%)	NR	
Asamiya [29]	28	4	1	23	3	1414.0 ± 759.2	9 (38%)	22 (96%)	NR	HT 11	21 cases: patent ductus: 3; RD: 4; retinopathy: 5; lung disease: 3; anaemia: 2; sepsis: 1; other: 3; brain haemorrhage: 1; death: 2
Chou [31]	10	1	3	6	1	1713 (1100–2388) IUGR 3 (33.3%)	3	Preterm 6 (100%) Early 4 (66.6%) Extreme 1 (17%)	NR	HT 4	NR
Jefferys [32]	5	0	0	5	0	2008 (467–2735)	2	Preterm 3 (60%)	NR	HT 2 PE 1	Ventricular defect: 1; retinopathy: 1
Bamberg [33]	5	0	0	5	0	1764 (1274–2465) IUGR 4 (80%)	3	Preterm 4 (80%)	5 (100%)	HT 3 PE 0	RD: 3; icterus: 3
Tan [36]	11	2	0	9	0	1390 ± 705.3 Low BW: 7 (77%) IUGR 3 (27.3%)	5	Preterm 9 (100%) Early 7 (77.7%) Extreme 1 (11%)	5 (56%)	HT 7	NR
Malik [37]	12	5	0	7	0	1700 (1115–2300); Low BW: 7 (100%) IUGR 8 (70%)	4	Preterm 7 (100%) Early 5 (71%) Extreme 1 (14%)	NR	PE 8	No congenital abnormalities
Eroğlu [38]	7	0	0	7	1	1400 (420–2640); IUGR 1 (14%)	4	Preterm 7 (100%) Early 3 (43%) Extreme 1 (14%)	NR	PE 3	RD: 1
Moranne [39]	7	1	0	6	1	1495 (660–1920); IUGR 2 (33%)	4	Preterm 6 (100%) Early 5 (83%) Extreme 1 (17%)	6 (100%)	HT 3	RD: 1; meconium ileus: 1; spastic paresis: 1
Bahloul [41]	12	7	0	5	NR	NR	NR	Preterm 4 (80%)	NR	HT 6	Anaemia: 4
Chao [42]	18	5	1	12	3	1542 (512–2660); IUGR 10 (77%)	6	Preterm 12 (100%) Early 7 (58%) Extreme 2 (17%)	NR	HT 13	No congenital abnormalities
Luciani [43]	5	0	1	4	0	1431 ± 738; low BW: 4 (100%) SGA 0	4	Preterm 4 (100%) Early 4 (100%) Extreme 1 (25%)	NR	HT 1	RD–retinopathy–cerebral palsy: 1; cardiomegaly–RD 1; death: 2

AKI, acute kidney injury; CKD, chronic kidney disease; w, weeks; NR, not reported; BW, birth weight; gw, gestational week; RD, respiratory distress; HT, hypertension; PE, pre-eclampsia; HD, haemodialysis; neo, neonatal; P, pregnancies; abort.: abortions (<24 gestational weeks); IUGR, intrauterine growth restriction; SGA, small for gestational age baby; CS, caesarean section; NICU, neonatal intensive care unit; HD pre, haemodialysis before pregnancy; HD in, start of haemodialysis in pregnancy.
[a]Sato 22 on HD.

Table 5. Case series: maternal characteristics, indications for delivery and other maternal outcomes in papers reporting them

Author [ref.]	Age (years)	Residual diuresis (24 h)	Conception before or on dialysis	Indications for delivery	Other maternal outcomes
Panaye [8]	28.5 ± 4	NR	24 dialysis, 2 before	NR	NR
Ståhl [9]	34.4 (28–41)	NR 3; others 1–2 L	1 dialysis, 4 before	IUGR: 2; foetal distress: 1; PROM: 1; PE: 1; previous CS and PE: 1	Post-partum haemorrhage: 2; hydramnios: 1; UTI: 1; heart insufficiency: 1. After delivery: transplant: 2
Hladunewich [10]	34 ± 4	NR	18 dialysis, 4 before	PE	Short cervix: 4; hydramnios: 1; chorioamnionitis: 1; PROM: 2; cerclage: 1
	27 ± 6	NR	57 dialysis, 13 before	NR	NR
Jesudason [12]	30.1 (26–32)	NR	53 dialysis, 24 before	NR	Gestational diabetes: 1; kidney transplant after delivery: 28; death: 4 (2.2–8.2 years)
Piccoli[a] [14]	31 (22–42)	Absent 10; Present 10 NR 1	19 dialysis, 4 before	Singletons: spontaneous: 8; PROM: 6; hypertension: 5; foetal: 2; HELLP: 1	After delivery: death: 2: intestinal infarction, cerebral haemorrhage (1–10 years)
Espinoza [15]	31.6 ± 3.8	NR	4 dialysis, 2 before	Cholestasis: 2; oligoamnios: 1; hydramnios: 1; IUGR:1	Hyperemesis: 3; oligoamnios: 1; hydramnios: 1
Zanlorenci [16]	30.4 ± 5.1 (18–42)	NR	15 dialysis, 13 before	NR	Hydramnios: 11; hypothyroidism: 6; diabetes: 5
Bernasconi [17]	30 ± 1	NR	26 dialysis, 11 before	Hypertension, polyhydramnios, PROM	Hydramnios: 16; HELLP: 1; death: 2 (post-partum). After delivery: transplant: 1, function recovery: 2, death: 1 (1 year)
Abou-Jaoude [20]	30 (22–33)	NR	5 dialysis; 2 before	IUGR: 1; oligoamnios: 1; foetal distress: 2	Hydramnios: 3, oligoamnios: 1
Macias [21]	26.3 ± 6	1.54 ± 0.811 L	27 before	NR	Peritonitis: 2
Hadj Sadek [22]	34 (24–45)	Absent 11	11 dialysis	For CS: foetal distress	All returned to their HD schedule after delivery
Sulaiman [23]	35 ± 5.9	NR	NR	NR	NR
Bahadi [24]	35 (22–40)	Absent 7 1.5–1 L (2)	8 dialysis, 1 before	NR	Anaemia: 9, polyhydramnios: 4
Luders [25]	29.7 ± 5.5	Median 1 L (0–3)	24 dialysis, 28 before	NR	Hydramnios or excess amniotic fluid: 21
Sato[b] [26]	30.2 (19–37)	NR	22 before	Hypertensive complications and/or foetal distress	Anaemia: 29; UTI: 2; PROM: 3. Outcome: transplant: 2; dialysis: 15; dialysis free: 3
Vázquez-Rodríguez [27]	Pre: 23.3 ± 1.5 dialysis: 35 ± 2.6	HD: 1.739 ± 0.26 L before: 3 ± 1.049 L	3 dialysis, 3 before	PE: 3; foetal distress: 2; renal function deterioration: 1	Anaemia: 6, hydramnios: 2
Boubaker [28]	32.8 (27–35)	NR	7 dialysis	NR	Anaemia: 6
Asamiya [29]	33.6 ± 4.3	NR	23 dialysis, 5 before	Vaginal: 11, foetal distress: 5, chorioamnionitis: 2; maternal: 1; HT: 3 CS: foetal: 6, poor progress: 1; maternal: 2	Hydramnios: 11, incompetent cervix: 4; hypotension: 1
Chou [31]	HD: 35.0 ± 4.3 (26–42)	Absent 5, NR 1; 0.3–0.9 L: 4	5 dialysis, 2 before; 3 PD	Only for CS: previous CS	Hydramnios: 6
Jefferys [32]	30 (19–35)	NR	5 before	Vaginal: hypertension caesarean: absent umbilical artery blood flow	Exit site infection: 3; malposition: 1; peritonitis: 1; diabetes: 1
Bamberg [33]	28 (21–37)	Absent 3	4 dialysis, 1 before	Umbilical Doppler: 2; underlying disease and SGA: 1	Premature contractions combined with cervical shortening: 3; preterm labour and hydramnios: 2
Tan [36]	28 (25–39)	NR	11 dialysis	HELLP, cholestasis, IUGR, PE HT, preterm labour, abruptio placentae	Hydramnios: 2; abruptio placentae: 1; pulmonary oedema: 1; PROM: 2; cholestasis:2; haemorrhage: 1; thromboembolism: 2; peritonitis: 1
Malik [37]	29 (20–37)	NR	5 dialysis, 4 before	Antepartum haemorrhage due to placenta previa	Uterine rupture: 1; hydramnios: 4; oligoamnios: 1. Outcome: transplant: 3; HD: 5; PD: 1
Eroğlu [38]	25 (22–31)	Absent 7	4 dialysis, 3 before	IUGR, PE, PROM, preterm labour	Polyhydramnios: 2; PROM: 2

Continued

Table 5. Continued

Author [ref.]	Age (years)	Residual diuresis (24 h)	Conception before or on dialysis	Indications for delivery	Other maternal outcomes
Moranne [39]	32 (22–39)	Absent 5; 0.6–1 L: 2	7 dialysis	PROM: 3; foetal distress: 2	Hydramnios: 5; post-partum haemorrhage: 1 Outcome: transplant: 4
Bahloul [41]	35 (25–44)	Absent 12	12 dialysis	NR	NR
Chao [42]	29 (22–43)	All absent or oliguria	17 dialysis, 1 before	Foetal distress, previous CS, breech, placenta previa, preterm labour, PROM	Hydramnios: 6; oligoamnios: 2; PROM: 4; premature contraction: 7; abortion-bleeding: 1. Outcome: dialysis (previous schedule)
Luciani [43]	27 ± 3.46	Absent 2, present 3	4 dialysis, 1 before	CS: abruptio placentae: 1; foetal distress: 3; vaginal: PROM	Hydramnios: 5; vaginal infections: 5

Duplicates not included; the most relevant paper is cited; when relevant information was available in a different paper on the same series, this was added to the table.
CS, caesarean section; HD, haemodialysis; HEELP, haemolysis, elevated liver enzyme levels, low platelet levels; HT, hypertension; IUGR, intrauterine growth restriction; NR, not reported; PD, peritoneal dialysis; PE, pre-eclampsia; PROM, premature rupture of membranes; SGA, small for gestational age; UTI, urinary tract infection.
[a]Only live births were included.
[b]Data on 22 cases.

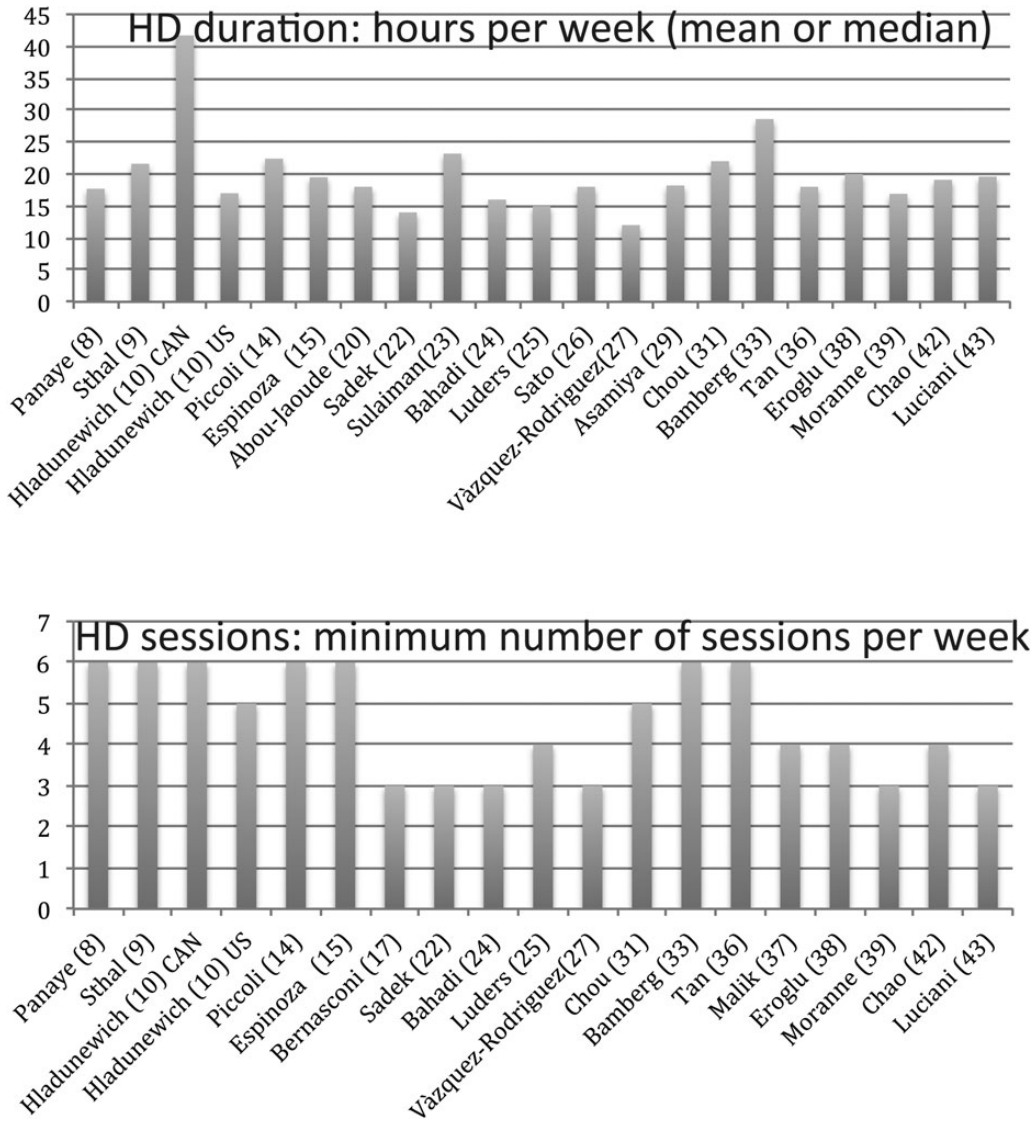

FIGURE 2: The distribution of hours of HD per week, and of minimum number of dialysis sessions, as measured in the papers reporting on them.

the lack of data on patient-years of observation impairs calculation of standardized mortality rates, with respect to the baseline risk in young dialysis patients [12, 14, 17].

The overall prevalence of SGA babies was 49/154, 32% (live births and stillbirths) in the relatively few series (only 6) reporting on this outcome on HD [9, 10, 14, 15, 20, 25]. Data on PD

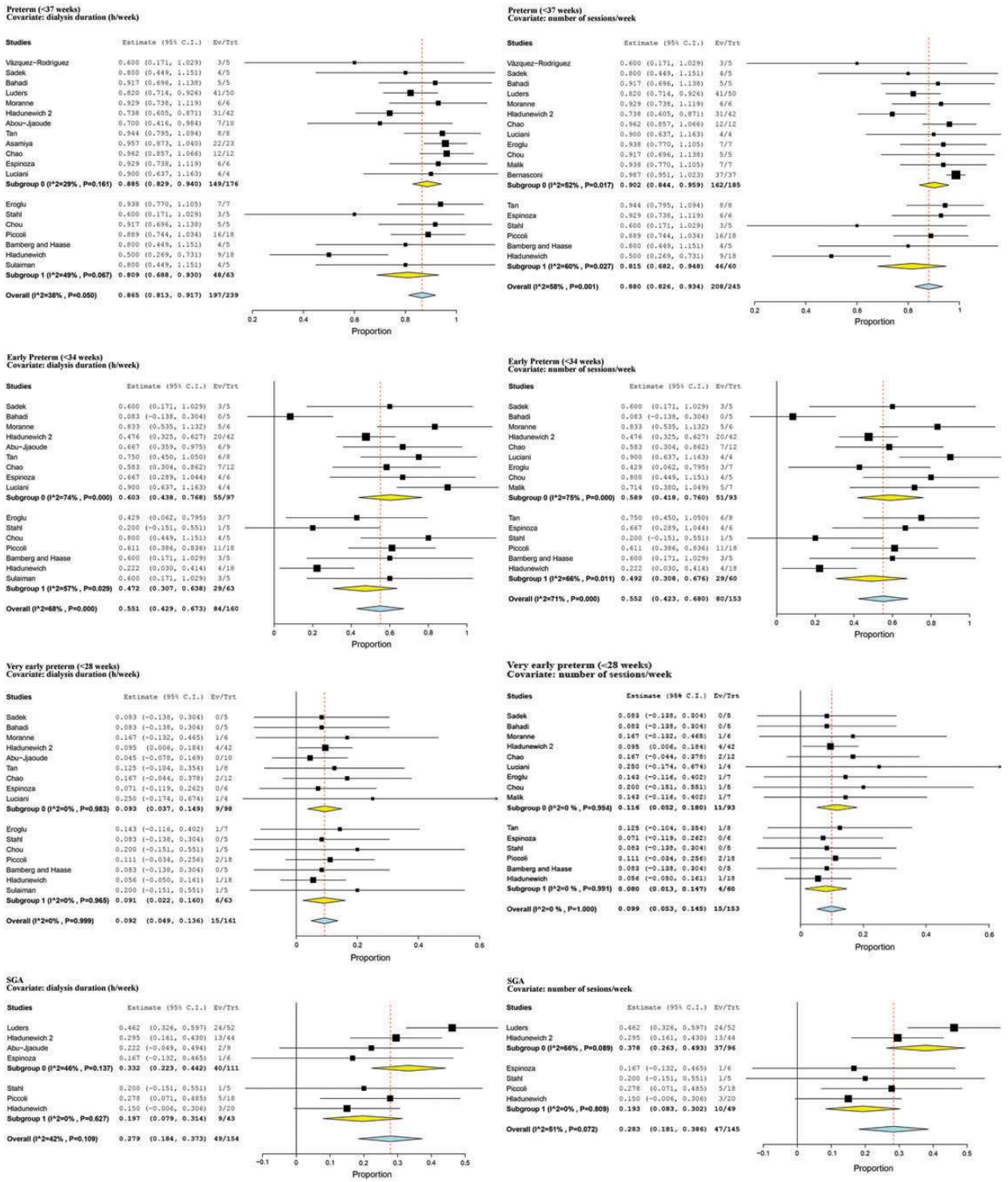

FIGURE 3: Forest plots depicting the relationship between dialysis duration (dichotomized at 20 h), dialysis sessions (dichotomized at six sessions), preterm, early preterm and very early preterm delivery and SGA.

are scant, and only two series report on SGA specifically in PD patients [2/3 in Piccoli and 10/27 in Marcias, overall 12/30 (40%)].

The prevalence of admission to the neonatal intensive care unit (69/119 children reported in 10 series on HD) was even more difficult to assess due to the heterogeneity of the indications (Table 4) [9, 10, 14, 17, 20, 22, 27, 33, 36, 39].

Meta-analysis: relationship between dialysis schedules and main outcomes

Various outcomes were evaluated including preterm, early preterm and very early preterm delivery (respectively, <37, <34 and <28 gestational weeks), and SGA.

While a trend towards better outcomes with more dialysis sessions and longer dialysis hours was observed in most of the cases,

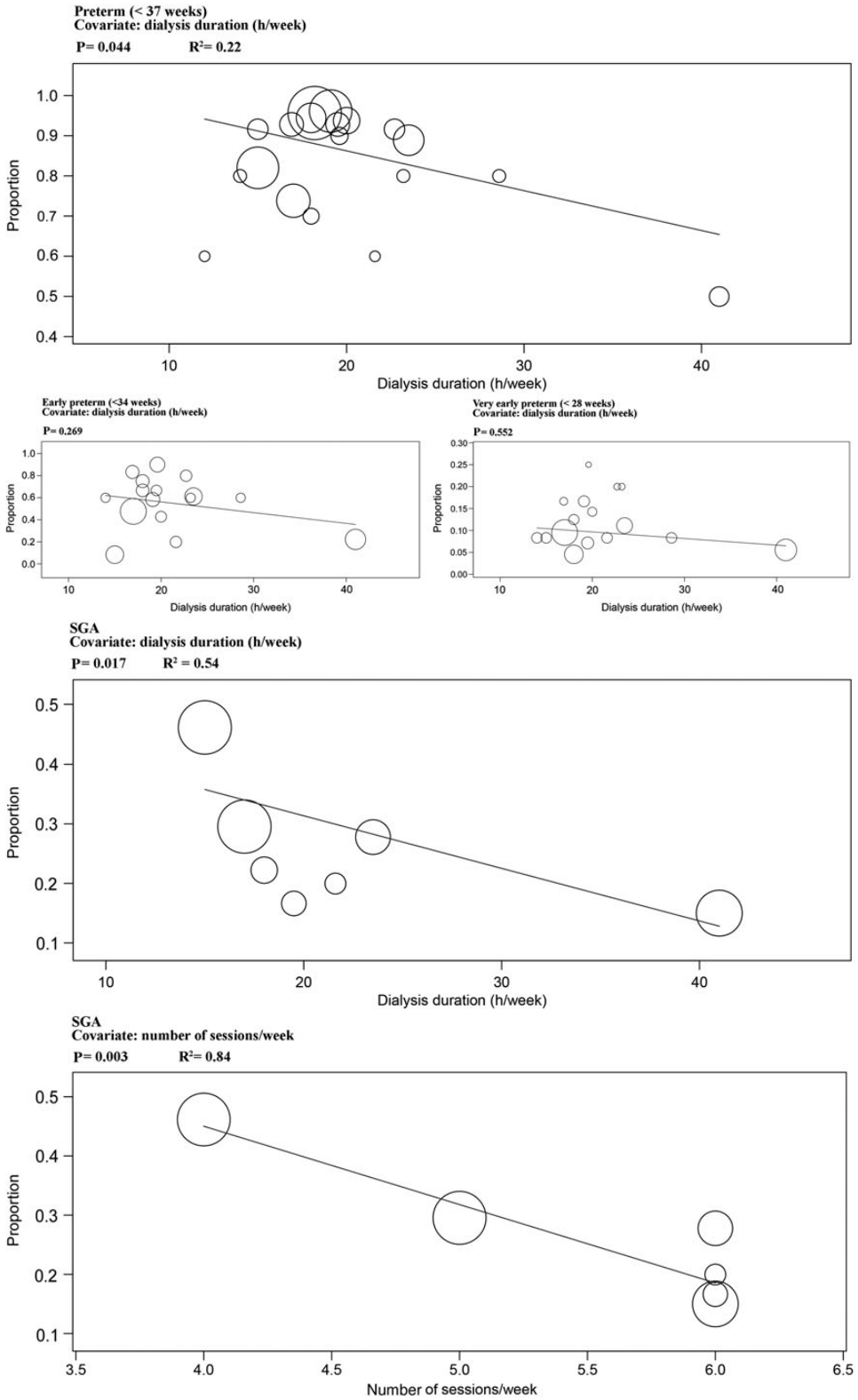

FIGURE 4: Meta-regression analysis depicting the relationship between dialysis duration (continuous, as measured in the paper), dialysis sessions (continuous, as measured in the paper), preterm, early preterm, very early preterm delivery and SGA. The circles represent the papers reporting on these outcomes, and their relationship is depicted by the regression line.

the differences are not statistically significant in the dichotomized analysis (Figure 3). Conversely, the pattern is consistent with a continuous effect reaching statistical significance in the meta-regression analysis with regard to weekly hours of dialysis (correlating with preterm delivery and SGA) and to the number of dialysis sessions (limited to SGA; Figure 4).

Table 6. Summary data: case reports: type of dialysis, main therapies and main maternal outcomes—complications

Groups	Age Median (minimum–maximum) parity	PE/other	Dialysis start median (minimum–maximum)	Diuresis	Dialysis: most used schedules (patients)	Maternal outcomes
HD: conception before HD start *N*: 35 ref: [53–82]	Age: 30 (18–39) Primi 6 (18%) Multi 19 (54%) NR 10 (28%)	HT 22 (63%) PE 2 (6%) Hydramnios 6 (17%) Anaemia 5 (14%) Oedema 4 (11%) UTI 4 (11%) Diabetes 2 (6%)	15.5 (4–30) GW	Present: 5 NR: 30	4 h × 6 days/w: 8 (23%) 3.5 h × 6 days/w: 3 (9%) 6 h × 6 days/w: 2 (6%) NR 6 (17%)	No deaths Other relevant: pelvic abscess (*Serratia*): 1 (3%); overwhelmed, depressed: 1 (3%); hypertension, pulmonary oedema: 1 (3%); NR: 11 (31%); dialysis independent: 1 (3%); kidney transplant: 1 (3%)
HD: conception after HD start *N*: 58 ref: [54, 63, 64, 70, 74, 78, 83–130]	Age: 32 (21–43) Primi 3 (5%) Multi 27 (47%) NR 28 (48%)	HT 28 (48%) PE 3 (5%) Hydramnios 12 (21%) Anaemia 9 (16%) Oedema 4 (7%) UTI 2 (3%) Hyperemesis 2 (3%)	5.5 (0–18) years before conception	Present: 10 Absent: 7 NR: 39	4 h × 6 days/w: 12 (21%) 4 h × 5 days/w: 5 (9%) 3 h × 6 days/w: 8 (14%) 3.5 h × 6 days/w: 4 (7%) 6 h × 6 days/w: 4 (7%) NR: 1 (2%)	No deaths Other relevant: cardiomyopathy: 2 (3%); hypertension: 2 (3%); heart failure: 2 (3%); ICU after delivery 1 (2%); NR: 20 (34%) dialysis independent: 1 (2%) kidney transplant: 2 (4%)
PD: all cases *N*: 14 ref: [55, 131–142]	Age: 27 (20–34) Primi 2 (14%) Multi 7 (50%) NR 5 (36%)	HT 8 (57%) PE 2 (14%) Hydramnios 2 (14%) Anaemia 4 (29%)	On PD: 10 (4–41) months before conception PD start: 19.6 (16–27) GW	Present: 6 Absent: 2 NR: 5	6 exchanges 1.5 L/day: 2 (14%) 5 exchanges 1.5 L/day: 2 (14%) Other or personalized schedule: 10 (71%)	No deaths Other relevant: none reported; dialysis independent: none; kidney transplant: 2 (14%)

For further details, refer to Supplementary data, Tables.
HD, haemodialysis; HT, hypertension; GW, week of gestation; ICU, intensive care unit; Multi, multipara; *N*, number; ref, references; NR, not reported; PE, pre-eclampsia; PD, peritoneal dialysis; Primi, primipara; UTI, urinary tract infection; w, week; ASA, acetylsalicylic acid; FSGS, focal segmental glomerulosclerosis; APDKD, autosomal dominant polycystic kidney disease; Diab. Neph., diabetic nephropathy; GN, glomerulonephritis; GNMP, membranous and proliferative glomerulonephritis; CPN, chronic pyelonephritis; MGN, membranous glomerulonephritis; HIVAN, HIV-related nephropathy.
Most common maternal diseases: HD: conception before dialysis start: FSGS: 3; IgA: 3; APDKD: 2; Diab. Neph.: 5; Goodpasture: 1; FBS: 1; GN: 1; interstitial: 1; Sjogren; 1; SLE: 2; hypertension: 2; reflux: 2; NR: 11. HD conception after dialysis start: ADPKD: 1; GNMP: 1; CPN: 1; Goodpasture: 1; Cystinosis: 1; Wegener: 1; vascular: 1; hypoplasia: 1; FSGS: 2; GN: 4; IgA: 3; MGN: 3; Diab. Neph.: 3; SLE: 8; hypertension: 4; reflux: 3; cortical necrosis: 3; idiopathic: 2; NR: 15.
PD: all cases: anti-GBM: 1; CPN: 1; obstructive: 1; HIVAN: 1; hypoplasia: 1; FSGS: 1; reflux: 1; vascular: 1; Diab. Neph.: 1; SLE: 2; NR: 3.
Geographical origin of the studies: HD: conception before dialysis start: Europe 9; North America: 13; Asia: 9; Africa: 2; South America: 1; Australia: 1. HD: conception after dialysis start: Europe 21; North America: 13; Asia: 14; Africa: 3; South America: 3; Australia: 3; NR: 1. PD: all cases: Europe 2; North America: 5; Asia: 5; Australia: 1; NR: 1.
Main drugs: HD: conception before dialysis start: antihypertensive: 19; EPO: 18; iron: 14 (3 oral, 10 iv, 1 NR); ASA: 3; heparin: 5; vitamins: 12. HD: conception after dialysis start: antihypertensive: 28; EPO: 40; iron: 26 (3 oral, 16 iv, 7 NR); ASA: 5; heparin: 25; vitamins: 22. PD all cases: antihypertensive: 5; EPO: 9; iron: 6 (4 oral, 2 iv); ASA: 1; heparin: 2; vitamins: 6 (vit D, multivitamins).

Case reports: overview

Tables 6 and 7 summarize the main features of the 117 pregnancies collected in the case reports: 35 pregnancies in patients who started HD after conception; 58 pregnancies in patients already on HD; and overall 14 pregnancies in PD patients [50–142]. The three groups were homogeneous for age at start of pregnancy (respectively, 30, 32 and 27 years, Table 6), and for gestational age (respectively, 33, 33 and 34 weeks). The dialysis schedules are similar to those reported in the series; however, the kidney diseases show a higher prevalence of systemic lupus erithematosus (SLE) and complex immunological disorders, in keeping with the selection bias of the case reports which are more prone to report on exceptional situations (cases: SLE: 12/78 excluding the non-reported diagnoses; SLE and other immunological diseases: 22/78 cases; series: SLE: 23/490 excluding the non-reported diagnoses and excluding duplicate publications).

No maternal deaths were reported in any of the three groups; it is, however, difficult to classify the other maternal complications due to the non-homogeneity of reporting; overall, about half of the patients were hypertensive in pregnancy, while the prevalence of pre-eclampsia (PE) is difficult to assess due to the frequent lack of definitions of the elusive 'superimposed' PE in chronic kidney disease (Table 6).

Case reports: relationship between dialysis schedule and outcomes

The prevalence of preterm delivery, early preterm delivery and very early preterm delivery is overall ∼80%, as reported in Table 8. The only significant difference observed in the analysis of the case reports is a higher prevalence of SGA on PD (66.7 versus 31% on HD; P = 0.015), in the context of a similar prevalence of preterm delivery and of a lower prevalence of very early preterm delivery (Table 8).

Table 7. Summary data: case reports: main foetal outcomes and indications for delivery

Groups	GW median (minimum–maximum)	NICU %	Infant outcomes: APGAR (1 and 5 min)median (minimum–maximum)	Weight (g) median (minimum–maximum)	IneS centile: median (minimum–maximum)	Delivery	Main indication for delivery
HD: conception before HD start *N*: 35 ref: [53–82]	33 (26–39)	Yes 43% NR 57%	APGAR 7 (0–9); 9 (4–10) Infant death 1 (3%) Major problems: RD (5), meconium aspiration (1), intracerebral bleeding and hydrocephalus (1), pneumatocele and sepsis (1), wet lung syndrome (1)	1803.5 (680–3500)	Centile: 39 (<1–98) SGA 17% AGA 66% LGA 3% NR 14%	CS 23 (66%) Vaginal 8 (23%) NR 4 (11%)	Foetal causes 7 (20%) (non-reassuring foetal tracing; IUGR; abnormal Doppler) Maternal causes 9 (26%) (HT; PE; placental abruption) Preterm labour 4 (11%), Other 3 (9%); NR 12 (34%)
HD: conception after HD start *N*: 58 ref: [54, 63, 64, 70, 74, 78, 83–130]	33 (23–40)	Yes 41% No 2% NR 57%	APGAR 7 (1–9) and 9 (3–10) Infant death 2 (2%) Major problems: RD (8), hyperbilirubinaemia (6), unilateral lung agenesis (1), meconium amniotic fluid (1), RD (1), retinopathy (1), nephrotic syndrome (1)	1700 (410–3505)	Centile: 25.5 (<1–100) SGA 33% AGA 47% LGA 10% NR 10%	CS 36 (62%) Vaginal 13 (22%) NR 9 (16%)	Foetal causes 16 (28%) (non-reassuring foetal tracing; IUGR; abnormal Doppler) Maternal causes 10 (17%) (HT, hydramnios, HELLP, placenta previa, placental abruption) Preterm labour 17 (29%) NR 15 (26%)
PD: all cases *N*: 14 ref: [55, 131–142]	34 (29–39)	Yes 29% No 15% NR 56%	APGAR 8 (3–10) and 9 (4–10) No infant deaths Major problems: RD (1), neonatal sepsis (1)	1780 (900–2700)	Centile: 7.5 (<1–57) SGA 57% AGA 29% NR 14%	CS 6 (43%) Vaginal 7 (50%) NR 1 (7%)	Foetal causes 3 (20%) (decreased foetal movements, IUGR) Maternal causes 2 (14%) (PE) Preterm labour 1 (7%) Other 2 (14%); NR 6 (43%)

For further details, refer to Supplementary data, Tables.
AGA, average for gestational age; CS, caesarean; GW, gestational week; HD, haemodialysis; HELLP, elevated liver enzymes low platelet; HT, hypertension; IUGR, intrauterine growth restriction; LGA, large for gestational age; NICU, neonatal intensive care unit; *N*, number; NR, not reported; PE, pre-eclampsia; RD, respiratory distress; ref, references; SGA, small for gestational age.

Table 8. Case reports: relationship between dialysis schedule and main outcomes

	SGA %			<37%			<34%			<28%		
	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value	Yes	No	P-value
PD	66.7	33.3	**0.015**	76.9	23.1	0.233	38.5	61.5	0.116	0	100	0.314
HD all cases	31.0	69.0		83.9	16.1		56.3	43.7		9.2	90.8	
HD: conception before HD start	20.0	80.0	0.130	78.1	21.9	0.414	50.0	50.0	0.495	9.4	90.6	0.295
HD: conception on HD	39.5	60.5		87.3	12.7		60.0	40.0		9.1	90.9	
HD: conception on HD												
<6 days	29.4	70.6	0.239	89.5	10.5	0.320	63.2	36.8	0.988	5.3	94.7	0.341
≥6 days	36.0	64.0		85.2	14.8		59.3	40.7		11.1	88.9	
HD: conception on HD												
<20 h/w	28.6	71.4	0.249	87.5	12.5	0.362	37.5	62.5	0.060	6.3	93.8	0.457
≥20 h/w	35.7	64.3		89.3	10.7		71.4	28.6		7.1	92.9	
HD all cases												
<20 h/w	26.1	73.9	0.863	84	16	0.223	44	56	0.137	4	96	0.283
≥20 h/w	27.5	72.5		90.2	9.8		65.9	34.2		9.8	90.2	
HD all cases												
<6 days	24.1	75.9	0.871	83.9	16.1	0.253	54.9	45.2	0.976	6.5	93.5	0.237
≥6 days	28.9	70.1		85.4	14.6		58.5	41.5		12.2	87.8	

For further details, refer to Supplementary data, Tables.
HD, haemodialysis; PD, peritoneal dialysis; SGA, small for gestational age; w, weeks.

DISCUSSION

The first result of this systematic review is the demonstration of an increasing interest in pregnancy on dialysis, as shown by the sharp increase in the number of reported cases, which went from 90 in the series retrieved by the same search strategy for the period between 2000 and 2008, to 574 pregnancies in 543 patients in the series gathered for the present analysis, 6 years later [4] (Table 1).

The picture derived from these studies is that of 'high-risk', difficult pregnancies, with a relevant, albeit poorly quantified

rate of early foetal loss, and a consistent risk of perinatal death (Tables 4–7). The high heterogeneity of the definitions prevents precise quantification of these risks; however, in the series, 63 perinatal deaths were reported in 352 pregnancies (18%, excluding early miscarriages).

Conversely, maternal perinatal mortality is very low (2/543 = 0.4%) and the incidence of malformations was ∼2% (7/448 major malformations reported in the series, and 2/107 in the case reports), in line with the risks recorded in the overall population (1–5%) [143–145]. Most of the problems reported in the newborns, namely respiratory distress, sepsis and retinopathy (Tables 4 and 7), are frequent consequences of prematurity and do not seem to be specifically related to the dialysis treatment in the mother [146–149].

Prematurity has a very high incidence in the reported cases and series; interestingly, the analysis of the single cases suggests that, in spite of a similar risk of prematurity, the prevalence of SGA babies may be higher in mothers on PD when compared with HD (Table 8). This finding is derived from case reports alone, which are more subject to publication, as well as to referral and reporting biases, and warrants confirmation on a larger scale [150–152].

Although the studies that were retrieved for this review shared the same limits that were already encountered in the previous review, mainly heterogeneity, lack of a control group and differences in definitions of relevant outcomes, such as perinatal deaths or PE, the large number of case series that were retrieved allowed for a meta-analytical approach at least for some of the more robust and clearly defined outcomes and for the better defined HD schedules [4] (Table 3).

In the case series, the two main determinants of HD schedule, dialysis frequency and dialysis duration, expressed as the number of hours per week, were significantly correlated with two major outcomes, i.e. prematurity and delivery of an SGA baby (Figures 3 and 4).

The number of HD hours per week was significantly correlated with preterm delivery (<37 completed gestational weeks) in the cohort of live-born babies and with delivery of an SGA baby; the latter is also significantly correlated with the maximum number of HD sessions per week (Figure 4). According to the meta-regression analysis, the effect is continuous, without an identifiable threshold; in keeping with this pattern, the differences do not reach statistical significance in the dichotomized analysis (Figures 3 and 4).

The main strength of our study is its novelty, together with the large number of retrieved cases: it is the first study to attempt a meta-regression analysis by correlating the main pregnancy outcomes and the main determinants of the dialysis schedule. Furthermore, the analysis also included single-case reports (up to four cases), and allowed us to formulate a hypothesis concerning the differences between the risks of HD and PD with regard to SGA babies (Table 8).

However, every systematic review also summarizes the limits of the current literature. Consequently, this review has several limitations: while a trend towards an inverse relationship between weekly hours on HD and early or extremely preterm delivery may be seen (Tables 1–5 and Figures 2–4), the flattening of the curves may reflect the rarity of the most severe events and the inclusion of live-born babies alone (thus losing the early perinatal losses, which are more frequent in early and extremely preterm deliveries). The choice of focusing on live-born babies was motivated by the lack of a univocal definition of prenatal and perinatal deaths; this limitation strengthens the importance of an unambiguous language in future studies [46].

For instance, there are several further important potential determinants of the outcomes: stratification was attempted for residual renal function, parity, age and maternal diseases, but the heterogeneity of the reports prevented further comparisons, once more suggesting the need for a common language in the future studies on pregnancy on dialysis and pregnancy. Not least, the high heterogeneity of the reports may play a confounding effect; we have tried to minimize it by choosing only papers published in the new millennium, but some studies include pregnancies from decades ago, when dialysis and perinatal care were remarkably different. Furthermore, we focused on cases already on dialysis, or who started dialysis in the first phase of pregnancy, thus losing potentially relevant information on the best timing for dialysis start, an important issue that should be addressed in further studies.

Within these limits, we feel that our study, which deals with a rapidly changing scenario, may have some practical importance in guiding preconception counselling and in defining the dialysis schedule after conception.

CONCLUSIONS

Pregnancy on dialysis is shifting from being an exception to being a rare, but not impossible event. The strict relationship between results and an intensive dialysis schedule forces the Nephrology community to deal with the new efficiency standard of quotidian, long-hour dialysis.

Our study may be partially reassuring with regard to the feasibility of pregnancy on dialysis through very demanding dialysis schedules and intensive check-ups. In this regard, the present evidence underlines also the importance of strong cooperation among specialists and between patients and physicians in order to ensure optimal results.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

The authors thank Valerie Perricone for her careful language assessment and also to the staff at the library of the ASOU san Luigi (Giuseppe Mauro and Natascia Castelluccia) for their valuable help in retrieving the selected papers. The study was accepted in abstract form at the 52th ERA-EDTA Congress (London 2015), and F.M., the presenting author, won a young investigator travel award. Study group on kidney and pregnancy of the Italian Society of Nephrology, Ex 60% to G.B.P.

AUTHORS' CONTRIBUTIONS

G.B.P. designed the study; G.B.P., G.C. and R.A. drafted the initial manuscript; G.B.P. and F.M. carried out the reference search, supported by N.C. who retrieved the evidence. Paper selection was carried out by G.B.P., and F.M. extracted the data; G.C., D.G. and A.R. participated in making the tables and in writing the final version of the manuscript. E.V. designed and performed the meta-analysis. A.P. and T.T. were assigned to the final check of the manuscript, respectively, from the Nephrologist's and Gynaecologist's point of view.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or in part, except in abstract format.

(See related article by Bramham. Dialysis and pregnancy: no longer the impossible. *Nephrol Dial Transplant* 2016; 31: 1763–1765)

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Received for publication: 2.9.2015; Accepted in revised form: 27.10.2015

Nephrol Dial Transplant (2016) 31: 1934–1937
doi: 10.1093/ndt/gfw311
Advance Access publication 1 September 2016

ORIGINAL ARTICLE

Solute solver 'what if' module for modeling urea kinetics

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ABSTRACT

Background. The publicly available Solute Solver module allows calculation of a variety of two-pool urea kinetic measures of dialysis adequacy using pre- and postdialysis plasma urea and estimated dialyzer clearance or estimated urea distribution volumes as inputs. However, the existing program does not have a 'what if' module, which would estimate the plasma urea values as well as commonly used measures of hemodialysis adequacy for a patient with a given urea distribution volume and urea nitrogen generation rate dialyzed according to a particular dialysis schedule.
Methods. Conventional variable extracellular volume 2-pool urea kinetic equations were used.
Results. A javascript-HTML Web form was created that can be used on any personal computer equipped with internet browsing software, to compute commonly used *Kt/V*-based measures of hemodialysis adequacy for patients with differing amounts of residual kidney function and following a variety of treatment schedules.
Conclusions. The completed Web form calculator may be particularly useful in computing equivalent continuous clearances for incremental hemodialysis strategies.

Keywords: dialysis adequacy, dialysis dose, hemodialysis, urea, urea kinetics

INTRODUCTION

One commonly used method to assess hemodialysis adequacy is urea *Kt/V* and, for other than 3/week schedules, an equivalent clearance calculated using a 2 pool analysis of urea kinetics, the standard *Kt/V* [1]. Two-pool urea kinetics is recommended for monitoring dialysis adequacy by the European Best Practices Group [2], and was used to both prescribe and analyze the dose of dialysis in the HEMO study [3–8] and in the Frequent Hemodialysis Network Trials [9–11]. As there was no publicly available, easy-to-use program to calculate urea kinetic outputs, the Solute Solver program was published and posted via the *American Journal of Kidney Disease* website [12] and at http://www.ureakinetics.org in 2009. Solute Solver allows easy calculation of urea kinetics based clearances using a variety of input strategies. One can input pre- and postdialysis blood urea nitrogen (BUN) values along with an estimated *in vivo* dialyzer urea clearance, e.g. as computed from *in vivo* dialyzer sodium clearance with an appropriate adjustment. Alternatively, the *in vivo* dialyzer urea clearance can be estimated by Solute Solver from the manufacturer's *in vitro* K_0A-urea value and blood and dialysate flow rates. One can also use the Casino approach [13] and input an estimated postdialysis urea distribution volume with the pre- and postdialysis BUN values, and then Solute