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Parenthood and pregnancy in Australians receiving treatment for end-stage kidney disease: protocol of a national study of perinatal and parental outcomes through population record linkage

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ABSTRACT

Introduction Achieving parenthood is challenging in individuals receiving renal replacement therapy (RRT; dialysis or kidney transplantation) for end-stage kidney disease. Decision-making regarding parenthood in RRT recipients should be underpinned by robust data, yet there is limited data on parental factors that drive adverse health outcomes. Therefore, we aim to investigate the perinatal risks and outcomes in parents receiving RRT.

Methods and analysis This is a multijurisdictional probabilistic data linkage study of perinatal, hospital, birth, death and renal registers from 1991 to 2013 from New South Wales, Western Australia, South Australia and the Australian Capital Territory. This study includes all babies born ≥20 weeks' gestation or 400 g birth weight captured through mandated data collection in the perinatal data sets. Through linkage with the Australian and New Zealand Dialysis and Transplant (ANZDATA) registry, babies exposed to RRT (and their parents) will be compared with babies who have not been exposed to RRT (and their parents) to determine obstetric and fetal outcomes, birth rates and fertility rates. One of the novel aspects of this study is the method that will be used to link fathers receiving RRT to the mothers and their babies within the perinatal data sets, using the birth register, enabling the identification of family units. The linked data set will be used to validate the parenthood events directly reported to ANZDATA.

Ethics and dissemination Ethics approval was obtained from Human Research Ethics Committees (HREC) and Aboriginal HREC in each jurisdiction. Findings of this study will be disseminated at scientific conferences and in peer-reviewed journals in tabular and aggregated forms. De-identified data will be presented and individual patients will not be identified. We will aim to present findings to relevant stakeholders (eg, patients, clinicians and policymakers) to maximise translational impact of research findings.

Strengths and limitations of this study

- This will be the largest study assessing robust data collected over 20 years across multiple jurisdictions in Australia, and will provide data beyond the limitations of current studies exploring births for parents with end-stage kidney disease.
- Renal registers lack detailed pregnancy data, while the perinatal data sets lack information about kidney disease, thus by linking these two data sets we will be able to evaluate pregnancy outcomes and perinatal risk factors associated with adverse outcomes in individuals with end-stage kidney disease.
- One of the novel aspects of this study is the method of linking fathers receiving dialysis or with a kidney transplant to the mothers and their babies within the perinatal data sets, using the birth register, enabling the identification of family units.
- Population data sets may inherently have inaccuracies. Birth register paternity data may not reflect biological paternity; therefore, some assumptions will be made regarding the biological paternity.

INTRODUCTION

Chronic kidney disease affects around 10% of the adults in the world[1] and up to about 3% of pregnant women.[2 3] Within Australia, among 25 652 individuals receiving renal replacement therapy (RRT; dialysis or kidney transplantation) for end-stage kidney disease (ESKD) at the end of 2018, 16% were in their reproductive age (18 to 44 years); 1760 women and 2397 men.[4] These individuals may have to consider significant and complex issues surrounding parenthood and pregnancy while receiving RRT.

For women receiving RRT, pregnancies are relatively uncommon and medically complicated.[5] Fertility rates are considerably lower in women receiving RRT than the general

population, particularly in women receiving dialysis; rates are improved, although not normalised, following kidney transplantation.[6–13] These pregnancies face higher risks of adverse outcomes for mothers and babies; notably, pre-eclampsia, hypertension, prematurity and low birth weight.[6 8 10 14]

The fate of infants born to women receiving RRT remains poorly defined during the perinatal period. Maternal factors (including comorbidities) and models of antenatal care are likely to be important determinants of pregnancy outcomes, yet there is little robust data on such factors with which to make informed decisions. There is also, as yet, lack of linkage between perinatal and renal data, as the Renal registers collect very limited pregnancy data, while the perinatal data sets lack information about maternal kidney disease. Therefore, having a linked data set containing both perinatal and renal data is important to aid exploration of outcomes and drivers of events.

Men receiving RRT are similarly subjected to impaired fertility, sperm production and lower sperm quality,[15 16] likely due to the uraemic environment. This commences in earlier stages of kidney disease and is not improved by dialysis.[17–19] Although fertility is largely restored post-transplantation, the long-term use of immunosuppressive medications (eg, mycophenolic acid) may have an impact on sperm production.[20] Currently, there is very limited data available about the outcomes of pregnancies fathered by men receiving dialysis,[21 22] with more data available for males after transplantation.[23–28] A key concern with individuals after kidney transplantation is the potential fetotoxic effects of immunosuppressive medications.[29] Previous studies have reported no negative impact on fertility or fetal outcomes with paternal mycophenolic acid exposure[23 24] or in males after kidney transplantation.[25] Despite this, there are still uncertainties in counselling about the use of mycophenolate derivatives in men considering parenthood.

Several previous studies within the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry have evaluated parenthood outcomes in female kidney transplant recipients. A study by Levidiotis *et al* assessing maternal and transplant survival rates following a live birth in female transplant recipients, from 1966 to 2005, found equivalent rates to non-pregnant women with a functioning transplant.[8] In this study, a decline in the absolute fertility rates over time in female transplant recipients was identified.[8] This was postulated to be due to counselling against pregnancy, impaired fertility and early pregnancy loss not reported to ANZDATA. A similar study by Wyld *et al* assessing parenthood events in female transplant recipients from 1971 to 2005 identified lower average gestational age, lower average birth weight and lower perinatal survival rate in babies born to mothers post-kidney transplantation compared with the general Australian population.[10] These pregnancies were also complicated by high rates of pre-eclampsia (30%). However, the majority of the pregnancies resulted in live birth.[8] In both of the studies above, live birth rates significantly improved over time, the rate of surgical terminations declined and the number of stillbirths and spontaneous abortions remained constant.[8 10] The perinatal mortality rate was six times higher in this cohort of female transplant recipients compared with the general Australian population. The rate of congenital abnormalities in transplant recipients was similar to the population rate (3% to 5%), although this may be an underestimation in the context of voluntary reporting.[10 13]

Several other studies within the ANZDATA registry have evaluated parenthood outcomes in women receiving dialysis. In contrast to transplant recipients, pregnancy rates in women receiving dialysis increased over time, particularly from 1996 to 2008.[6] This may be due to intensive dialysis treatment and other improvements in medical and obstetric care. Live birth rates were lower in women receiving dialysis (~60%), compared with transplant recipients, although this gap narrowed after the exclusion of early terminations (~75%).[6 7] High rates of pre-eclampsia (19.4%) were noted in women receiving dialysis. The majority of the babies born to women receiving dialysis were preterm (<37 weeks' gestation) (53%) and had a low birth weight (65%).[6 7] Women who conceived prior to commencing dialysis had higher live birth rates compared with those who conceived after starting dialysis (91% vs 63%), while the babies had similar distribution of gestational age and birth weight. This was postulated to be due to better residual renal function (higher estimated glomerular filtration rate at chronic dialysis commencement) in the cohort who commenced dialysis during pregnancy.

There are concerns regarding the reporting of parenthood events to the ANZDATA registry, due to the voluntary nature of reporting, that need to be explored through comparisons with the legislated perinatal data sets. While it is possible to establish birth outcomes, fetal adverse events (eg, intrauterine growth restriction) and maternal medical complications (eg, pre-eclampsia), obstetric and perinatal data that is essential in understanding these outcomes is limited within the ANZDATA registry, although it is available in state-based perinatal data sets.

Studies that have explored perinatal outcomes for individuals with ESKD to date have been limited. Additional clinical data is required for better identification of risk factors for the higher rates of adverse outcomes previously identified. Outcomes for twin babies, causes underlying perinatal deaths and long-term outcomes of preterm babies born to parents receiving RRT still remain to be investigated. Obtaining information about babies of fathers who received RRT is valuable, however, ANZDATA registry does not collect data on mothers (not receiving RRT) for paternity parenthood events, nor does it follow-up the babies of parents receiving RRT in the long-term. To overcome these challenges, we will conduct a data linkage between a number of data sets including the ANZDATA registry and state-based perinatal data sets.

Aims and hypotheses

The aim of this study is to explore the association of RRT with pregnancy outcomes, antenatal and perinatal outcomes, compared with the non-RRT population.

1. **Fertility, birth rates and paternity rates:** To report birth rates and fertility rates of mothers receiving RRT compared with mothers who have either never received RRT or have given birth prior to commencement of RRT, and paternity rates of fathers receiving RRT.
2. **Validation of ANZDATA parenthood data collection:** To compare parenthood events identified through the data linkage to those directly reported to the ANZDATA registry.
3. **Maternal outcomes:** To quantify the excess maternal risks for pregnancies such as maternal morbidity during pregnancy, labour and birth, maternal resource utilisation in women receiving RRT compared with women who have never received RRT and those who are receiving RRT without pregnancy.
4. **Fetal outcomes:** To investigate the effect of maternal or paternal ESKD requiring RRT on perinatal and health of neonates such as birth status, prematurity, birth weight, neonatal intensive care unit admission, length of hospital stay and congenital anomalies.
5. **RRT and parenthood:** To evaluate parental factors specific to RRT which may be important determinants of outcome for babies born to parents receiving RRT.

We hypothesised higher rates of maternal morbidity in women receiving RRT compared with the women who have never received RRT during pregnancy. It is thought that babies of men receiving RRT will have better outcomes than babies born to women receiving RRT, and similar to the general population.

METHODS AND ANALYSIS

Study design

This study is a retrospective cohort study that uses state-level data linkage of records from 01 January 1991 to 31 December 2013 from perinatal, hospital, emergency, birth, death and renal register data (ANZDATA) in New South Wales (NSW), Western Australia (WA), South Australia (SA) and the Australian Capital Territory (ACT). Follow-up data will be available for all babies beyond 31 December 2013 and up until the latest data set available at the time of data linkage.

Study population and inclusion criteria

The study population includes all babies born at least 20 weeks' gestation or 400 g birth weight between 01 January 1991 and 31 December 2013, captured within the perinatal data sets from each jurisdiction, except for NSW and ACT where the perinatal data sets are only available from 01 January 1994 and 01 January 1997, respectively. Within the study population, all babies born to women after commencement of RRT will be identified as the maternal RRT birth cohort, while all other babies born to mothers who have either never received RRT or have given birth prior to commencement of RRT will be identified as the maternal non-RRT birth cohort. Some women within the maternal RRT birth cohort may have conceived prior to commencing dialysis. Transplantation does not occur during pregnancy. Babies fathered by men after commencement of RRT will be identified as the paternal RRT birth cohort and analysed separately. If the father was not receiving RRT at conception (based on calculated/estimated conception date), the baby will be in the paternal non-RRT birth cohort. The ANZDATA registry collects information from all patients receiving RRT where the intention to treat is long-term. This study defines receiving RRT as those patients with RRT treatments reported to ANZDATA. The ANZDATA registry does not collect cases of RRT for acute kidney injury that resolves. Pregnancies in ANZDATA females will be identified through named linkage to perinatal data sets. Babies born to ANZDATA males will be identified through named linkage to birth registers. The mothers associated with babies of ANZDATA males will be flagged within the non-RRT birth cohort to allow family units to be identified. Early pregnancy loss including miscarriage or termination of pregnancy <20 weeks' gestation are not captured in the perinatal data sets.

Key outcomes of interest

Maternal outcomes

1. General obstetric complications and maternal comorbidity during pregnancy (gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes, antepartum/postpartum haemorrhage, placental abruption and praevia).
2. Labour and birth outcomes (type of onset of labour, indication for induction, type of birth, elective caesarean section, indication for caesarean section, analgesia administered, complications of labour, transfusion post partum).
3. Maternal resource utilisation methods (admissions during antenatal period, hospital length of stay immediately pre-delivery and post-delivery, maternal readmission within 4 weeks post-delivery, place of birth, mode of hospital separation, intensive care unit admission).

Fetal/neonatal outcomes

1. Birth outcomes (Birth status (live birth vs stillbirth), neonatal and perinatal deaths, neonatal intensive care unit admission, gestational age and its categories, birth weight and its categories).
2. Infant outcomes (Activity, pulse, grimace, appearance and respiration (APGAR) scores, resuscitation at birth, neonatal morbidity, length of hospital stay, readmission and congenital anomalies).

Linked data sets

Third party linkage units (table 1) will perform the probabilistic linkage of records (figure 1) based on

Table 1 Summary of perinatal data sets by different states in Australia

State	Perinatal data collection	Numbers of births 1991–2013 (approximately)	Years for linkage	Linkage unit
NSW	NSW PDC	1 900 000	1994–2013	CHeReL
ACT	ACT PDC	100 000	1997–2013	CHeReL
WA	WA Midwives' Notification System	630 000	1991–2013	Data linkage WA
SA	SA Perinatal Statistics Collection	440 000	1991–2013	SA/NT Datalink

ACT, Australian Capital Territory; CHeReL, Centre for Health Record Linkage; NSW, New South Wales; NT, Northern Territory; PDC, perinatal data collection; SA, South Australia; WA, Western Australia.

name, date of birth and postcode and generate de-identified project master linkage keys for each matched record.

Perinatal data

Data on pregnancy and childbirth are reported to the perinatal data sets in each jurisdiction in Australia, by midwives and other birth attendants. Data collection is mandated for all births ≥20 weeks' gestation or ≥400 g birth weight. Data on demographic information of the mother and baby, models of antenatal care, pregnancy outcomes, maternal comorbidities during pregnancy, labour and birth outcomes, maternal resource utilisation and fetal outcomes are collected. Perinatal data sets are different and independent in each jurisdiction. The maternity information matrix has identified similar data items collected across each jurisdiction and this will be used for pooling data for analysis.[30]

ANZDATA registry

Established in 1977 from existing dialysis and transplant registers with data collections from 1963, ANZDATA receives clinical data annually for patients receiving RRT from all renal units in Australia and New Zealand with follow-up reporting rates for the annual survey approaching 100%. The ANZDATA registry introduced a specific parenthood form in 2001 to formalise data collection on parenthood events in both males and females receiving RRT, which has been expanded to include additional clinical questions for the 2019 survey. It is one of the largest registers in the world, with more than 2000 pregnancies reported since the inception of the register, and more than 1000 pregnancies and more than 900 live births reported during 1991 to 2013. Importantly, ANZDATA captures all pregnancy events including those ending <20 weeks' gestation. The ANZDATA parenthood form enables the collection of data on maternal complications of diabetes and pre-eclampsia and pregnancy outcomes including early terminations and stillbirths, gestational age, birth weight, presence or absence of fetal abnormality and neonatal mortality, but only limited data is available. The cohort of men and women who ever received RRT during 1970 to 2016 will be linked to perinatal data sets.

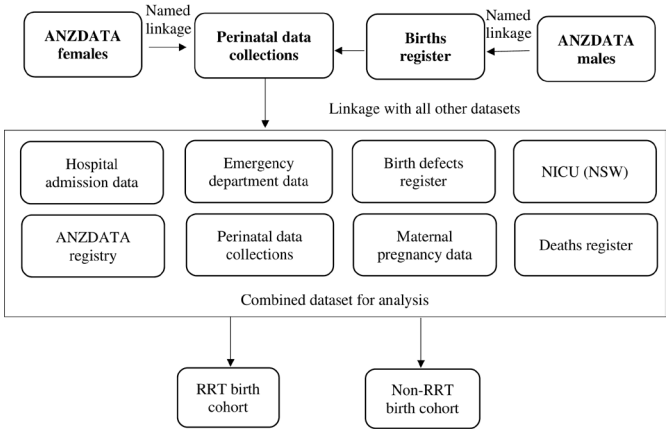

Figure 1 Data sets to be linked. ANZDATA, Australia and New Zealand Dialysis and Transplant registry; NICU, neonatal intensive care units; NSW, New South Wales; RRT, renal replacement therapy.

Births and deaths registers

Data sets that register details of all births and deaths in each jurisdiction will be used for identification of the birth cohort and analysis of death rates. Birth register will enable the identification of family units by linking fathers receiving RRT to babies and their mothers.

Hospital separation and admitted patient data

This data set captures hospital attendance and diagnostic coding data from all mothers and babies admitted to hospitals for treatment during pregnancy and after birth. Comorbidity and health events in the perinatal period and also following childbirth can be evaluated, through admission rates and diagnostic codes attributed to these admissions.

Emergency department data

This data set captures emergency department presentations with disease codes and enables evaluation of the overall healthcare burden for babies born to mothers receiving RRT.

Neonatal intensive care units (NSW only)

This data set collects short-term and neurodevelopmental data for neonates admitted to neonatal intensive care units within 28 days of birth and enables comparisons of adverse events, treatments and outcomes between

neonates born to mothers receiving RRT and other preterm neonates.

Births defects register

This is a register that collects details of congenital anomalies at birth. Birth defects registers from SA and WA will be used for this study. For NSW and ACT, birth defects registers will not be used as data is only available for a small 5-year window, instead the admitted patient data captures the birth defect information more accurately for these jurisdictions. This data will enable us to determine if there is a higher rate of birth defects and congenital conditions in neonates born to mothers receiving RRT.

Comparator cohort

The comparator cohort includes all babies born to mothers who have either never received RRT or have given birth prior to commencement of RRT, captured within the perinatal data sets from each jurisdiction. Some of the events investigated in this study are very uncommon or rare in the general cohort, but clinically relevant and thought to be statistically different in the RRT birth cohort. Therefore, the entire comparator cohort is required to avoid introducing any selection bias. The planned analyses will require different control cohorts (much smaller subset of the full control cohort) for comparison, depending on the endpoint being evaluated and risk factors for that endpoint, therefore a single sampling of the maternal non-RRT birth cohort is unlikely to be representative.

Patient and public involvement

Our previous systematic review[31] and interview study[31] established the perspectives and preferences of women with chronic kidney disease. Women thought parenthood is a priority but causes significant decisional conflict and guilt, exacerbated by medical catastrophising.[31] From this we developed a framework for pregnancy counselling, with shared decision-making forming the central tenet of care.[31] Leading on from this prior work we have established a national consumer advisory group in Australia consisting of six women with kidney disease. This consumer advisory group have provided and will continue to provide us insights into their lived experiences and real-world issues most relevant to them and their families. They can also raise awareness and advocate about consumer priorities. In the future, this consumer advisory group will provide feedback on written work, assist us in preparing consumer friendly summaries for dissemination of key research findings into the community and develop future research questions.

Planned statistical analysis

Descriptive techniques, relative risks of variables, survival (time-to-event) analysis with survival curves and mortality trends for high-risk infants will be used. Excess risk will be determined by calculation of standardised incidence ratios. Multivariate analysis will determine odds ratio/relative risk of maternal and perinatal outcomes, adjusted for parental demographic and RRT-related parameters such as parental age, comorbidities and era of treatment. The effects of multiple births by a single parent will be accounted for using multilevel mixed effect models. Outcomes for the RRT and non-RRT birth cohorts will be compared via standard techniques (χ^2 tests, Student's t-test, Fisher's exact tests, multivariate logistic regression and linear regression) as appropriate. Analyses will be performed using Stata V.16.0. Detailed analysis plan is outlined below and variables of interest are summarised in table 2.

Table 2 Summary of obstetric, maternal and infant variables of interest

Variables of interest	
Demographic characteristics	► Age at conception ► Ethnicity ► Primary renal disease ► Socio-economic indexes for areas ► Smoking status ► Total duration of RRT ► Duration of latest modality of RRT ► Body mass index ► Pre-existing diabetes and hypertension
Antenatal factors	► Parity ► Previous caesarean section ► Gestational age at first antenatal visit ► Number of antenatal visits ► Types of antenatal tests
Fetal variables	► Plurality ► Sex of baby

RRT, renal replacement therapy

Analysis 1 and 2

The number of births to parents in the RRT and non-RRT birth cohorts will be quantified. The RRT cohort will be divided into different treatment modalities (dialysis or transplant) at time of conception. Parents receiving haemodialysis or peritoneal dialysis at conception will be defined as the dialysis RRT birth cohort, while parents with a functioning kidney transplant at conception will be defined as the transplant RRT birth cohort. Birth outcome (live birth, stillbirth or neonatal death) for each cohort will be described using descriptive statistics. Crude birth rate, age-specific fertility rates and age-specific paternity rates for each cohort will be calculated using the equations below and will be compared between the RRT and non-RRT birth cohorts.

$$Crude\ birth\ rates = \left(\frac{Total\ no.\ of\ births\ (Live\ and\ stillbirth)\ in\ each\ cohort}{Total\ population\ in\ each\ cohort}\right) \times 1000$$

$$Age-specific\ fertility\ rates = \left(\frac{No.of\ live\ births\ to\ women\ in\ each\ age\ group}{Estimated\ population\ of\ women\ in\ each\ age\ group}\right) \times 1000$$

$$Age-specific\ paternity\ rates = \left(\frac{No.of\ live\ births\ to\ men\ in\ each\ age\ group}{Estimated\ population\ of\ men\ in\ each\ age\ group}\right) \times 1000$$

Total fertility rates (the average number of live births per woman) will be calculated as a sum of 5-year age-specific fertility rates per 1000 women (live births at each age of women per female population of that age). The 3-yearly moving average of fertility rates will be also calculated from fertility rates in the current year, previous year and next year. Each parenthood event identified from the data linkage will be validated with the parenthood events directly reported to ANZDATA to identify any parenthood events not reported to ANZDATA directly and to identify any potential linkage errors.

The population estimates for the RRT birth cohort during 1991 to 2013 will be obtained from ANZDATA, as this will be the total number of patients receiving RRT in each jurisdiction during this time period. The population estimates for the non-RRT birth cohort will be calculated as the total population of each jurisdiction during 1991 to 2013 from the Australian Bureau of Statistics less the RRT population from each jurisdiction.

Analysis 3

The excess risks for pregnancies in women receiving RRT, compared with the non-RRT group, will be quantified by evaluating pregnancy outcomes; antenatal events and delivery complications; events contributing to preterm delivery; short-term postpartum obstetric, medical and surgical events and complications and outcomes including hospital length of stay, rates of readmission and reasons for readmission by calculation of standardised incidence ratios. Multivariate analysis will be used to determine odds ratio/relative risk of outcomes of interests listed above, with adjustments for parental demographic and RRT-related parameters such as parental age, comorbidities and era of treatment.

The long-term morbidity burden of mothers with ESKD including hospitalisations will be assessed using multivariate logistic regression, adjusting for potential confounding factors such as maternal age and era of treatment. The pregnancy outcomes and morbidity in women receiving RRT will be compared with women who have never received RRT using a multivariate logistic regression, with adjustments for maternal age and era of treatment.

Analysis 4

The relationship of parental RRT with perinatal and health of babies will be analysed by evaluating birth status and condition at birth; rates of prematurity, low birth weight and small for gestational age; intensive care or special care nursery admission data; presence and nature of congenital anomalies; hospital admission, morbidity and mortality data in the perinatal period and to 5 years of age and differences between preterm babies born to RRT parents and preterm babies born to non-RRT parents using either multivariate linear regression (for continuous data) or multivariate logistic regression (for categorical data), with adjustments for parental age, comorbidities and era of treatment. For each data item the denominator will be adjusted to account for the variation in different data collection periods in different registers.

Analysis 5

Parental factors specific to RRT including age, primary renal disease, comorbidity, RRT modality, duration of therapy, immunosuppressive drug exposure and kidney transplant function, which are likely to be important determinants of outcome, will be evaluated by estimating relative risks using multivariate regression models for the outcome of live birth. Analyses will be adjusted for potential confounding factors such as parental age, era of treatment and comorbidities.

Ethics and dissemination

Ethics approval was obtained from the NSW Population and Health Services Human Research Ethics Committee (HREC), NSW Aboriginal Health and Medical Research Council HREC, Department of Health WA HREC, WA Aboriginal Health Ethics Committee, SA Department for Health and Wellbeing HREC, SA Aboriginal HREC, ACT Health HREC and Calvary Public Hospital HREC. De-identified linked data sets will be stored on secure servers at the Royal Adelaide Hospital, Adelaide, South Australia, with access granted only to research staff. The results of this study will be published in peer-reviewed journals and presented at scientific conferences. No individual participants will be identified or identifiable. All data will be analysed and presented in the de-identified form. We will aim to present findings to relevant stakeholders (eg, patients, clinicians and policymakers) to maximise translational impact of research findings.

DISCUSSION

The current study explores the maternal and fetal outcomes of parents receiving dialysis or transplant for ESKD, compared with the general Australian population. For the first time nationally in Australia, this study will provide population evidence on the maternal and paternal factors, obstetric factors and perinatal risk factors associated with adverse pregnancy and fetal outcomes in individuals receiving RRT during pregnancy. Improved understanding of factors driving adverse outcomes will contribute to improving clinical management, especially if some factors are preventable.

Despite the strengths of the study, there are some potential limitations. Since the data used in the study is not collected for research purposes, quality and completeness may be limited. In addition, birth register paternity data may not reflect biological paternity for both the RRT and non-RRT birth cohorts. However, a subgroup of fathers receiving RRT who have had births also reported to the ANZDATA parenthood register will have confirmed biological paternity as this is an inclusion criterion for this

register. For all other births not reported to ANZDATA, assumptions are made regarding the biological paternity. With respect to sperm donation as a potential confounder for paternity, the data sets in this study will not be able to identify offspring from sperm donation. However, these events are uncommon, therefore the influence on the data is likely to be small. Nonetheless, the current study will be one of the first studies to explore perinatal risks and outcomes in the Australian population at a national level.

Overall, the data obtained from this study will inform future health policy and planning for this high-risk cohort, to assist clinicians in counselling and better managing patients who are considering or are faced with parenthood while receiving RRT.

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Contributors SJ, SPM, ES and PAC designed the study and research questions. SJ, SPM and PAC developed the statistical analysis plan. EH and SJ completed the first draft of the manuscript. EH, AG, CED, ES, SW, PAC, SPM and SJ reviewed the manuscript and provided input to the final draft.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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