Pregnancy during dialysis: still a challenge to get there, but worth the effort

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‘I knew that the transplant would change my life, and I wanted that kidney. But I wanted a baby a lot more, and from that point I knew that my life was going to be so much more amazing because of him’ (http://www.lhsc.on.ca/About_Us/LHSC/Publications/Features/pregnancy_on_dialysis.htm). The statement of a young woman on haemodialysis who became pregnant thanks to a 6-days-a-week haemodialysis scheme and who had been told 10 years earlier when she started chronic dialysis treatment that she was unlikely ever to become pregnant and that trying to was also not to be advised as pregnancy would most probably further compromise her fragile health (http://www.lhsc.on.ca/About_Us/LHSC/Publications/Features/pregnancy_on_dialysis.htm). This clearly illustrates the impact of unattainable maternity for young women on dialysis. An Australian review on women’s perspectives for pregnancy in chronic kidney disease (CKD) describes that ‘pursuing motherhood is fulfilling an innate or social desire to have a child and that not achieving this is also often experienced as a failure to fulfil social terms, undermining their self-worth’ [1]. Yet, even today, most commercial sites discourage pregnancy for patients on dialysis by reason of the presumed risks for mortality or severe comorbidity in the offspring, and official guidelines (KDIGO, NICE) are lacking.

Achieving maternity is indeed still a challenge for women with CKD. As the disease progresses, sexual desire and fertility decline, but once pregnant also the chances for an adverse outcome of mother and child increase. CKD of any stage is associated with a 5-fold increased risk for fetal and 2-fold for maternal complications. Patients with CKD stages 3–5 are especially at risk for fetal loss, prematurity and pre-eclampsia [1–6].

Until recently, the chances for pregnancy while on dialysis were considered to be nearly non-existent. The incidence of conceptions in women on dialysis has increased since the report of the first successful pregnancy in 1970 from 0.9% in the 1980s to 2% in the 1990s and 7% in more recent reports [7, 8]. Most concerning, however, was the outcome of such pregnancies as less than 50% resulted in survival of the baby, which is the reason why until recently so little effort has been undertaken to improve fertility in these women.

Giorgina Piccoli and others undertook a review on all published pregnancies in women on dialysis in 2010 and found only 90 reported pregnancies in 78 patients reported between 2000 and 2008 with a heterogeneous picture with respect to outcome [4]. At the same time, they saw a significant trend towards a more strict surveillance of pregnant women on dialysis and a parallel improvement of outcomes over the last years. Close control of urea (levels <17 mmol/L), phosphate, bicarbonate (>20 mmol/L), avoidance of hypocalcaemia, anaemia (>10 g/dL or 6.8 mmol/L) and especially of maintaining an normal blood pressure, adequate folate supplementation, adaption of protein to 1.5 g/kg with 20 g supplementation for fetal growth and calorie intake and avoidance of teratogen drugs, such as ACEi and MMF after transplantation are recognized as important measures [4, 9].

The combined implementation of frequent dialysis regimes to 20–36 h per week and close maternal–fetal monitoring has been a breaking improvement in the surveillance of pregnancies during dialysis. An increase in the conception rate up to 15% has been described in patients on frequent haemodialysis. Recent reports from the ANZDATA registry confirm an increase in pregnancies of women on dialysis over the last decades as well as an increase in the number of live births to 79% [5].

In a case report on a 31-year-old woman, conversion from conventional HD to five to six times 7 h nocturnal haemodialysis resulted in return of normal menstrual cycles after 8 months and pregnancy after 2 years with delivery of a healthy 3025 g child at 38 weeks’ gestation [10]. Another case report showed similar outcomes on three times per week 8 h HD under strict...
surveillance of blood pressure, uraemic toxins and antiangiogenic factors [11] resulting in a healthy term child of 2480 g. In a larger Canadian study, 22 pregnancy outcomes in the Toronto Pregnancy and Kidney Disease Clinic and Registry (2000–2013) of women on 43 h of dialysis on average per week were compared with those of 70 pregnancies in women from the American Registry for Pregnancy in Dialysis Patients (1990–2011) who had been on 17 h dialysis per week [12]. The Canadian group was superior by all means to the American cohort showing a live birth rate of 86.4 versus 61.4%, a birth weight of 2118 g (2417.5 for the five patients on nocturnal HD) versus 1748 g and a mean pregnancy duration of 36 weeks in women who were on at least 36 h per week dialysis versus 27 weeks in the American cohort. They also demonstrated a significant dose response association between dialysis intensity and pregnancy outcome; those who had been on nocturnal haemodialysis for 36 h per week had the best outcomes in terms of maternal complications, duration of pregnancy, birth weight and fetal complications [12, 13]. These favourable outcomes have been confirmed by a few other, mostly case reports, but data remain incredibly sparse in this field [9, 14–17].

There are some case reports on pregnancy in women on peritoneal dialysis (PD) with relatively good outcome of the pregnancy as compared to conventional HD, but in most larger registry cohort studies, no significant advantage of PD over haemodialysis was found in percentage of conception, nor in outcome of the pregnancy; according to the ANZDATA, patients on PD were less likely to achieve pregnancy compared to HD [5, 18–20].

The last concern was on how these children would develop in the long run. Giorgina Piccoli and others have followed 24 babies born from 23 women on dialysis. Three patients had been on PD and 20 were on bicarbonate dialysis or haemodiafiltration. The most common change during pregnancy was an increase in dialysis frequency; the most common schedule was 4 h six times per week. Most deliveries were premature; the mean pregnancy duration was 30 weeks. Three babies died within 3 months after birth all with birth weights of 1200 g or less. All others survived with no apparent problems [21].

In this edition, the same group reports on the emotional and behavioural profile of the same cohort of children and compared them with mothers treated for hereditary forms of microcytæmia such as transfusion-dependent beta-thalassemia. The mean age of the offspring at the time of assessment was 8.5 years (2–23 years). Although nearly 65% had needed NICU admission and 29% had been small for gestational age, only 5.9% had a height of less than −2SD and nearly 12% a weight of less than −2SD. Educational attainment was in the normal range for all children of on-dialysis mothers; two children were reported to have socialization problems. On all behaviour domains, children of on-dialysis mothers scored similar to healthy controls, except for a slightly higher score on pervasive developmental problems, comparable with outcomes seen in other premature born children. Mothers with microcytæmia more often reported emotional and behavioural problems than dialysis mothers. A striking finding was the very low degree of parental stress among the dialysis mothers when compared with healthy controls and microcytæmia mothers. The authors indicate that dialysis mothers also scored low on the PSI subscale, which is supposed to be indicative for a defensive response. This could be explained as the result of a tendency to deny problems, something that has been described before in dialysis patients. Yet, it could also be a genuine reflection of a strong personality of people who have suffered and learned to deal with problems.

It is hard to draw firm conclusions from these sparse data, but the outcomes of the current Italian study are not fully unexpected after the good results of the Toronto experience. It shows that maternity in dialysis is still hard to achieve and once obtained warrants an intensive surveillance, but may in the end result in a healthy baby with good prospects and a very happy mother. That is a hopeful message.

## CONFLICT OF INTEREST STATEMENT


## REFERENCES

Infections have been a major complication in patients with end-stage renal disease (ESRD) ever since maintenance haemodialysis was introduced. However, the problem is not limited to dialysis patients alone. An estimated glomerular filtration rate (eGFR) <45 mL/min 1.73 m² leads to strongly enhanced rates of hospitalization for infectious complications [1] and the risk of infection increases linearly with decreasing renal function, at least in patients aged 65 years or older. This is most likely a consequence of impaired immune function occurring with the retention of uraemic toxins. Deficient function has been described for neutrophils, monocytes and T-lymphocytes [2, 3]. In particular, granulocytes have impaired phagocytic activity [4], a finding with major relevance for bacterial infections. In addition, many patients with chronic renal failure have diabetes mellitus or receive immunosuppressive therapy for autoimmune diseases. Quite expectedly, the number of genitourinary infections increases with decreasing renal function. However, pulmonary infections are even more frequent and also bacteraemia contributes measurably [1].

The risk for blood-stream infection (BSI) is enhanced in patients with chronic kidney disease (CKD) not on dialysis. A Canadian study [5] evaluated a clinical laboratory database and found that CKD 4 tripled the risk of bacteraemia compared to individuals with eGFR >60 mL/min 1.73 m². While *Escherichia coli* was the predominant pathogen in CKD 3, *Staphylococcus aureus* took over in CKD 4 [5]. These aspects need to be kept in mind when reading the literature on blood stream infections in dialysis patients.

There are numerous publications pointing to high rates of BSI in haemodialysis patients [6–8]. The majority of them show a predominant role of *S. aureus* to the risk of bacteraemia [7]. Among the most important determinants for BSI is the type of dialysis access—whether a catheter or a fistula is in use [6, 8]. Central venous catheters (CVCs) associate with an 8-fold increase in the risk for bacteraemia [6]. This may be an important factor contributing to the enhanced mortality risk that the DOPPS study found for patients being treated by catheter rather than fistula [9]. A recent large analysis confirmed impressively that starting dialysis treatment with a catheter rather than a fistula strongly predicts the risk of bacteraemia [10]. In addition, starting with a catheter also predicts continued use of a catheter as dialysis access at 1 year. More than 13% of all patients had at least one positive blood culture within 1 year of dialysis initiation, the risk being 3-fold higher in catheter compared to fistula patients [10]. Interestingly, the probability of catheter-related bacteraemia seems to be age-related [11]. Surprisingly, the elderly had lower rates of BSI than the younger patients, which might be related to less physical activity in the former.

Still, the problem of BSI may be largely underestimated in every day clinical work. Dialysis doctors see single cases and since BSI remains an infrequent incident they usually do not have a feeling for the incidence in their dialysis programme. Nevertheless, it is alarming that cardiologists already identified haemodialysis as an important predisposing condition for the development of bacterial endocarditis [12]. Again, *S. aureus* is