Nephrol Dial Transplant (2023) 38: 148–157
https://doi.org/10.1093/ndt/gfac051
Advance Access publication date 3 March 2022

ORIGINAL ARTICLE

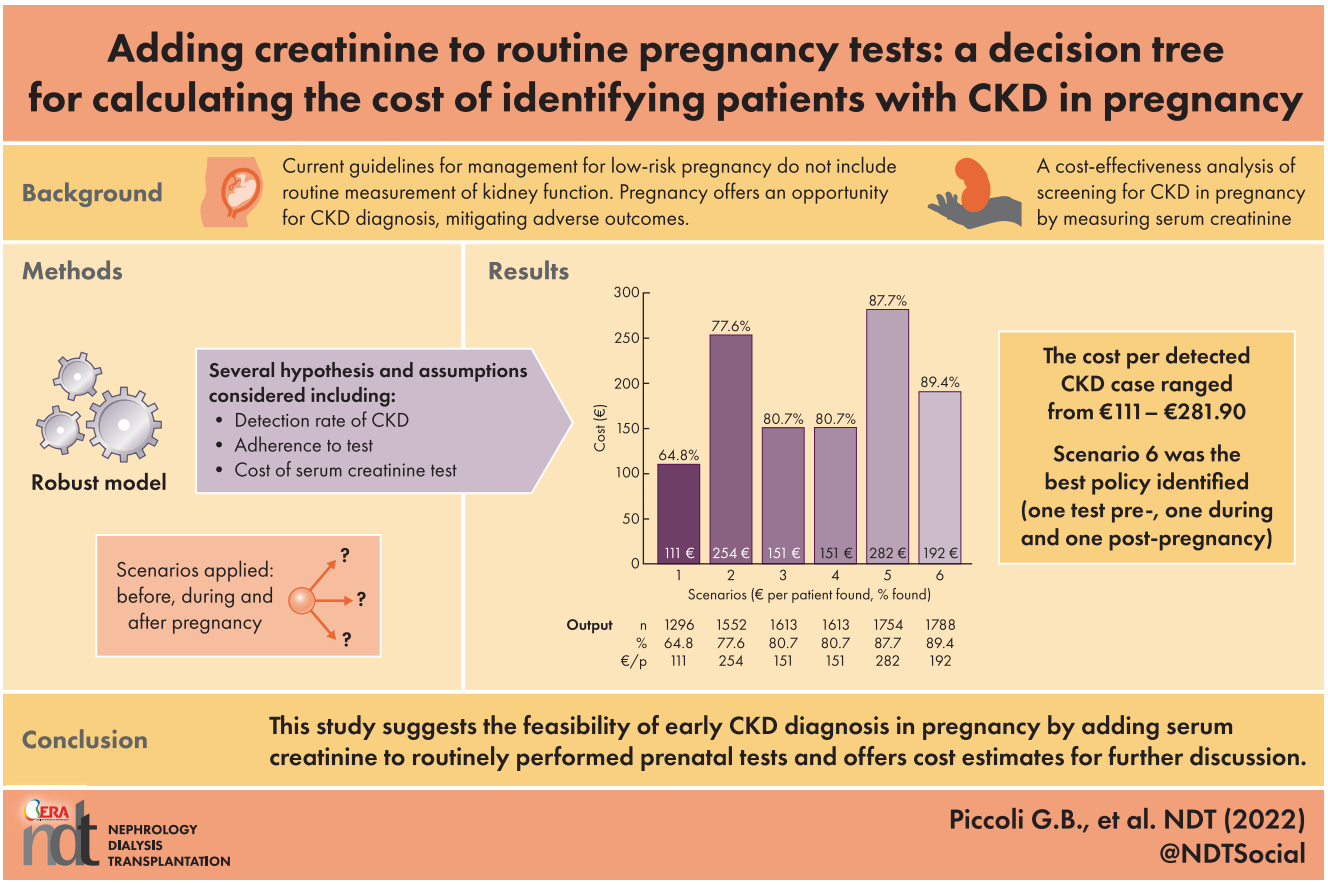
Adding creatinine to routine pregnancy tests: a decision tree for calculating the cost of identifying patients with CKD in pregnancy

Giorgina Barbara Piccoli[1], Antoine Chatrenet[1,2], Manuela Cataldo[3], Massimo Torreggiani[1], Rossella Attini[4], Bianca Masturzo[4], Gianfranca Cabiddu[5] and Elisabetta Versino[6]; Kidney and Pregnancy Study Group of the Italian Society of Nephrology

[1]Néphrologie et dialyse, Centre Hospitalier Le Mans, 194 Avenue Rubillard, Le Mans, France, [2]Laboratory "Movement, Interactions, Performance" (EA 4334), Le Mans University, Le Mans, France, [3]Department of Nephrology, University Aldo Moro, Bari, Italy, [4]Department of Obstetrics and Gynecology, Città della Salute e della Scienza, Ospedale Sant'Anna, University of Torino, Turin, Italy, [5]Nephrology, Azienda Ospedaliera Brotzu, Cagliari, Italy and [6]Epidemiology, Department of Clinical and Biological Sciences, University of Torino, Turin Italy

Correspondence to: Giorgina Barbara Piccoli; E-mail: gbpiccoli@yahoo.it

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Chronic kidney disease (CKD) is a risk factor for preeclampsia and up to 20% of women who have experienced preeclampsia are thought to have underlying CKD, which frequently fails to be diagnosed.
- The European guidelines for routine prenatal care do not include serum creatinine testing to screen for CKD.
- Universal screening for CKD in pregnancy is increasingly being advocated by the nephrology community.

What this study adds?

- A cost-effectiveness analysis of screening for CKD in pregnancy by measuring serum creatinine.

What impact this may have on practice or policy?

- Early CKD diagnosis could improve mother and fetal outcomes during pregnancy.
- Early CKD diagnosis could improve women's health in the long term.

ABSTRACT

Background. Even in its early stages, chronic kidney disease (CKD) is associated with adverse pregnancy outcomes. The current guidelines for pregnancy management suggest identifying risk factors for adverse outcomes but do not mention kidney diseases. Since CKD is often asymptomatic, pregnancy offers a valuable opportunity for diagnosis. The present analysis attempts to quantify the cost of adding serum creatinine to prenatal screening and monitoring tests.

Methods. The decision tree we built takes several screening scenarios (before, during and after pregnancy) into consideration, following the hypothesis that while 1:750 pregnant women are affected by stage 4–5 CKD and 1:375 by stage 3B, only 50% of CKD cases are known. Prevalence of abortions/miscarriages was calculated at 30%; compliance with tests was hypothesized at 50% pre- and post-pregnancy and 90% during pregnancy (30% for miscarriages); the cost of serum creatinine (production cost) was set at 0.20 euros. A downloadable calculator, which makes it possible to adapt these figures to other settings, is available.

Results. The cost per detected CKD case ranged from 111 euros (one test during pregnancy, diagnostic yield 64.8%) to 281.90 euros (one test per trimester, plus one post-pregnancy or miscarriage, diagnostic yield 87.7%). The best policy is identified as one test pre-, one during and one post-pregnancy (191.80 euros, diagnostic yield 89.4%).

Conclusions. This study suggests the feasibility of early CKD diagnosis in pregnancy by adding serum creatinine to routinely performed prenatal tests and offers cost estimates for further discussion.

Keywords: chronic kidney disease, hypertensive disorders of pregnancy, pre-term delivery, preeclampsia, screening

INTRODUCTION

Chronic kidney disease (CKD) is a risk factor for adverse pregnancy outcomes even in the early stages of the disease [1–3]. However, while the current European and US guidelines for the management of low-risk pregnancy include a search for major risk factors such as diabetes and hypertension, they do not include measuring kidney function [4–6]. While most guidelines recommend including questions on diabetes, hypertension and thyroid diseases, none specifically mentions determining whether a patient has a history of kidney disease or suggest testing kidney function before or at the beginning of pregnancy, thus failing to acknowledge that CKD is often asymptomatic and may not be found unless searched for [7–9]. Although dipstick urinalysis, the only test routinely prescribed in pregnancy, serves to identify kidney diseases characterized by proteinuria, its limits as a sole marker of kidney disease are well known and this test is probably more important, during the second half of pregnancy, for identifying preeclampsia [4–7]. Attention to microscopic haematuria can increase the diagnostic yield of urinalysis, but, since it is found in up to 20% of uneventful pregnancies, its association with CKD is loose in this setting [10].

By definition, CKD encompasses any abnormality of kidney structure or function [glomerular filtration rate (GFR) measured or calculated] or blood and urine composition, including alteration in blood or electrolytes [11]. Thus, CKD diagnosis requires a combined assessment of kidney function and electrolytes, renal imagery and urinalysis. A urinalysis alone cannot detect reduced kidney function, kidney malformations and scars, interstitial nephropathies and glomerulonephritis in remission unless they are associated with proteinuria, which is not common in these conditions [12].

Many, if not most kidney diseases are asymptomatic and awareness of having CKD is reported to be low, reaching 80% in patients treated in nephrology, but often lower than 10% in the general population and reaching at most 50% in the most advanced CKD stages (stage 3–5) [13–17]. Pregnancy is often the first time that biochemical tests are performed on an asymptomatic young woman; in this context, assessment of the kidney function can identify patients with asymptomatic CKD and indicate pregnancies that require particular attention, allowing the timely provision of care and better outcomes [18–21].

On the occasion of the 2018 World Kidney Day dedicated to women and kidney diseases, the integration of serum creatinine, a simple, low-cost, widespread and pivotal marker of kidney function, in the work-up for pregnant patients was suggested as a potential tool for improving women's health [22]. To date, this suggestion has not been widely followed.

Table 1. Main assumptions for the calculation of costs and references

Item	Chosen values	Note
CKD prevalence in childbearing age: all cases all stages	3% (1–5%)	Classic estimate, in line with recent meta-analyses [25, 26, 27]. May be higher in developing countries [18, 19, 21].
CKD prevalence in childbearing age: stages 4–5	0.133% (0.05–0.50%) 1:750	Classic estimate, in line with recent meta-analyses [25, 26]. May be higher in developing countries [18, 19, 21].
CKD prevalence in childbearing age: stage 3b	0.267% (0.1–1%)	Extrapolation from [25, 26]. Twice as frequent as stages 4–5. May be higher in developing countries.
Known CKD	50% (5–80%)	Literature data. Lower in early CKD stages, reaches 80% only in nephrology settings, but is reported to be lower than 50% even in late stages, in patients not followed in nephrology [13–17]. Data on women of childbearing age are lacking.
Detection rate of CKD	90% stages 3b–5 (80–95%)	Detection rate conservatively assessed, considering the variability in creatinine assessment [28]. Detection rate may be higher before and after pregnancy. Adjustment is needed for correct interpretation in pregnancy, but we did not consider the recent indications on adjustment, as they are not fully acknowledged in clinical practice [23, 24].
Cost of serum creatinine tests	0.10–0.20 euros per added test 1.00–1.50 euros per self-standing test	Cost of tests depends on technique (Jaffe, enzymatic) and number of tests per laboratory. Average data from hospital laboratories in the setting of study (unpublished data from the hospital management).
Number of tests per pregnancy	1–5 tests	According to prescription: pre-; each trimester; post-pregnancy (empirically tested, according to the pregnancy control schedules [4–7].
Adherence to tests	50% pre- and post- pregnancy (20–60%); miscarriages: 30% (20–40%); at least one test in pregnancy (70–95%)	Literature data [29, 30–32]. May be lower in developing countries, or where the cost of the test is not reimbursed.
Abortion–miscarriage rate	30% (10–45%)	Literature data [33–35]. Prevalence merges voluntary pregnancy terminations (20–50%) and miscarriages (8–15%). The first depends significantly on cultural and religious settings, and varies from country to country.

In the present study, we calculated, modelling data available from the literature, how much detecting new CKD cases with reduced kidney function would cost, adding serum creatinine to pregnancy screening and monitoring tests, in several scenarios. Due to the changes in glomerular filtration rate in pregnancy, creatinine levels must be interpreted with caution; acknowledging this, we conservatively modelled our decision tree focussing on the detection of cases with a relevant reduction in kidney function (CKD stage 3b onwards) [23, 24].

MATERIALS AND METHODS

Baseline hypotheses

The model discussed here is based on the following series of assumptions (Table 1):

- The prevalence of CKD in pregnant women is the same as in women of childbearing age. We relied on Davison's classic estimate that sets CKD at about 3% in this population and estimates the prevalence of 'severe' CKD to be 1:750 [25]. This was considered as synonymous with a prevalence of CKD stages 4–5 (0.13333% of the population). As for stage 3, considering that the prevalence is usually estimated to be 4–10 times higher than CKD stages 4–5, we hypothesized that it was evenly divided between stages 3a and 3b and focussed only on stage 3b [estimated GFR (eGFR) 44–30 mL/min], to account for the difficulty in detecting lesser degrees of a creatinine increase in pregnancy [23, 24]. We conservatively estimated prevalence as double that of stages 4–5 (i.e. 0.26667% of the population). The estimate is conservative and in line with a large recent meta-analysis [26].
- Targeting the model to the detection of cases with reduced kidney function, we hypothesized that a patient with CKD stage 3b before pregnancy (eGFR 30–44 mL/min) would remain in stage 3, possibly shifting to 3a (eGFR 59–45 mL/min), during pregnancy. This choice is quite conservative: we did not consider the possibility of detecting earlier stages (1–3a), if serum creatinine were to be adjusted for pregnancy and urinalysis and hypertension were considered [24, 25].
- Having set the detection threshold at relatively low eGFR levels, we considered that a further 10% of cases would escape detection because of laboratory errors (detection rate of 90%). Laboratory errors were broadly defined as any defect from ordering tests to reporting and interpreting results [36]. With respect to serum creatinine, a 10% variability was retained after discussion with the head of our laboratory, situated in one of the three largest non-university hospitals in France. This estimate is in keeping with a recent study on delta checks of serum creatinine in the laboratory context, highlighting the overall high reliability of serum creatinine laboratory assessment [37]. This is a very conservative, empiric estimate that includes pre-analytical errors (such as non-fasting test, hyperhydration or under-hydration); laboratory variability

(analyser-related); unacknowledged differences among different laboratory tests employed (Jaffé, enzymatic).

- We did not consider 'false positives' because, even with a 20% decrease in GFR (corresponding to the highest variability of serum creatinine tests), these cases would have an eGFR < 60 mL/min and warrant evaluation, in the very conservative diagnostic setting we had chosen.
- Our proposal regards the inclusion of serum creatinine in standard outpatient controls that are advised in the absence of signs and symptoms of the disease. In the case of severe infection, persistent fever, severe hyperemesis or other diseases potentially causing pregnancy-related acute kidney injury (AKI), serum creatinine should be routinely measured and followed up at least to full normalization. AKI and CKD are intrinsically linked and attention to AKI can lead to early CKD diagnosis [20–22]. As we lacked epidemiological data, we did not consider this event in the present model.
- We did not consider the diagnostic yield of urinalysis in detecting forms of CKD characterized by proteinuria, nor did we consider haematuria, due to its high prevalence in pregnancy [10]. While we used conservative figures for all other items, given the lack of data on the prevalence of CKD stages 3b–5 and proteinuria in pregnancy, we did not try to adjust for the prevalence of cases that would have been detected by proteinuria.
- We assumed that 50% of the patients would not be aware of the presence of CKD [13–16], a figure that is probably underestimated, as recent studies in the US set CKD unawareness at higher than 90% of cases, even in the late stages of the disease and found higher levels of awareness only in patients being followed in a nephrology setting [13–16]. No data exist on the awareness of CKD in younger patients, but it is known that awareness increases with kidney function impairment and, since we focussed on relatively late CKD stages, we once more chose a very conservative figure.
- The abortion/miscarriage rate, adherence to tests and detection rate (based on standard laboratory error for serum creatinine) were modelled on the data in the literature (Table 1).
- We chose a rounded cost of 0.20 euros per serum creatinine test, considering, in the European setting, that the test would be added to the ones fully covered by the patient's healthcare system and performed consensually (costs per test evaluated at 0.10–0.30 euros). The cost per diagnosis, therefore, represents the direct cost covered by the healthcare system. Since we hypothesized that the test would be performed consensually with ones that had already been prescribed during the course of pregnancy, indirect costs borne by the patient (loss of working time, transportation, etc.) or by the structure (personnel for blood sampling, etc.) were not added [38].

Building the model

Considering that the assumptions listed above, though justified by the scientific literature, are subject to variations based on socio-economic and cultural settings, in order to be consistent with the natural history of the disease and the standards of care in European countries and at the same be adaptable to other settings and contexts, we decided to use a simplified flexible model derived from a decision-tree approach [39]. The model was developed using Microsoft Excel 2016 and is downloadable as Supplementary data. The spreadsheet is modifiable and makes it possible to adapt costs and baseline hypotheses to different clinical and socio-economic models of care.

The robustness of the cost-effectiveness analysis was tested through a deterministic one-way sensitivity analysis model, limited to the least expensive/most efficient scenarios.

The model identifies the variation in costs per case detected according to variations in the following factors: CKD prevalence in childbearing age for stages 4–5; the prevalence of known CKD; detection rate of CKD; cost of serum creatinine tests; adherence to tests; abortion rate (see Table 1).

Results are presented as a tornado chart: for each variable considered, the chart shows the estimate of the base, lowest and highest cost, assuming that all the other variables are stable (i.e. they remain at baseline value) [40, 41].

RESULTS

Identification of the number of cases to be detected

According to the data in the literature (Table 1), we hypothesized there would be 30 000 cases with CKD per million pregnant women. Considering a prevalence of stages 3b–5 of 0.40% (4000 cases), half of which were known, we modelled the detection of 2000 cases with unknown CKD per million pregnancies, rounded ignoring correction for the sake of simplicity (1 000 000 – 2000 known cases = 998 000; 1996 cases to be detected). The assumptions leading to the calculation of the number of cases that would be found, reported in Table 1, are graphically plotted in Figure 1.

Analysis of different scenarios

The assumptions reported in Table 1 and Figure 1 were applied to six different scenarios combining tests before, during and after pregnancy (Table 2).

The cost per new diagnosis, calculated according to our basic assumptions (Table 1, Figure 1), considering a production cost of 0.20 euros per creatinine test, is reported in Figure 2, which is also the graphic output of the calculation sheet available online (supplementary data). While, understandably, the simplest scenario (one test during pregnancy) is the least expensive, it detects less than two-thirds of the cases; the best performance combines one test before pregnancy, one test during pregnancy and one test after delivery (expected, based on our assumptions, to detect almost 90% of the cases).

The flow chart of scenario 6, which has the highest diagnostic yield for an intermediate cost (191 euros per new diagnosis), is reported in Figure 3.

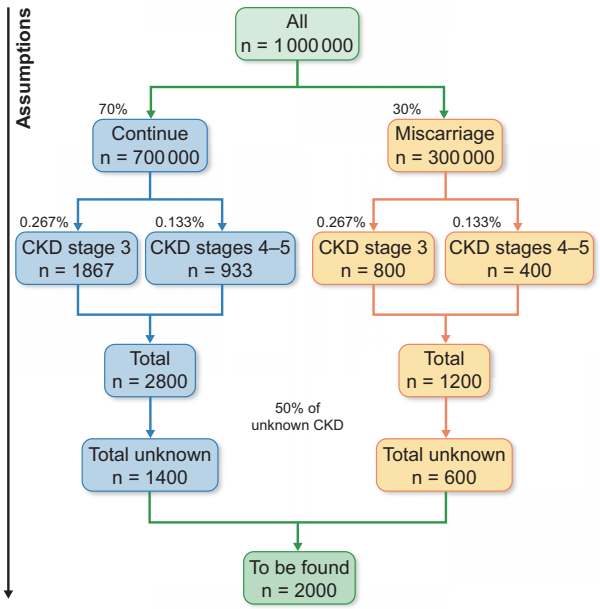


FIGURE 1: Flow-chart of the main assumptions leading to the identification of the number of cases that would be found.

Table 2. Different scenarios and their diagnostic yield

	Scenario 1:	Scenario 2:	Scenario 3:
N tests	One test performed during pregnancy (prescribed in the first trimester)	One test in the first trimester, repeated if normal, in each trimester	One test pre-pregnancy, 1 test during pregnancy
N cases detected	1296	1552	1613
Diagnostic yield (expected 2000)	**64.8%**	**77.6%**	**80.7%**
	Scenario 4:	**Scenario 5:**	**Scenario 6:**
N tests	As scenario 1 plus 1 test post-pregnancy or post-miscarriage	As scenario 2 plus 1 test post-pregnancy or post-miscarriage	As scenario 3 plus 1 test post-pregnancy or post-miscarriage
N cases detected	1613	1754	1788
Diagnostic yield (expected 2000)	**80.7%**	**87.7%**	**89.4%**

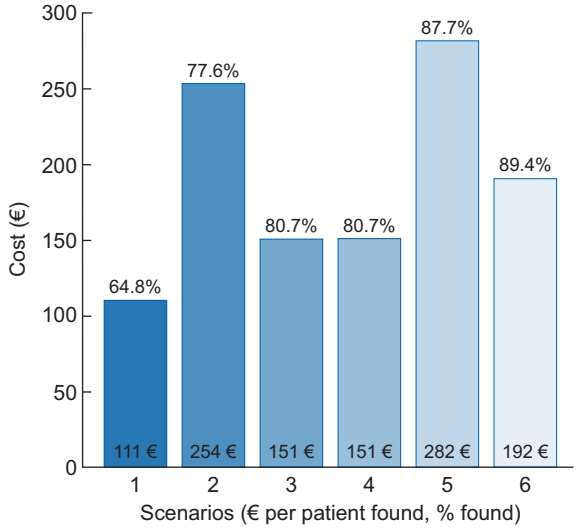
Sensitivity analysis

As reported in Figure 4, the data on which our model was built show a high degree of variability, which results from the high heterogeneity of the source studies. In terms of economic yield, the impact on cost is relevant and is mainly modulated, beyond the cost of the test itself, by the prevalence of unacknowledged CKD and by the prevalence of miscarriages and pregnancy terminations. In the input page of the downloadable calculator, shown in Figure 5, all assumptions are modifiable and changing them leads to variations in the output page.

DISCUSSION

Early diagnosis of CKD is an often mentioned and rarely pursued goal. No single test is able to detect all cases of CKD, whose diagnosis often requires integration between blood and urine tests and renal imaging [12]. Therefore, a screening policy is deemed to represent a compromise between an interest in discovering as many cases as possible and the feasibility and cost of blood, urine and imaging tests.

Pregnancy is in a delicate balance between being a physiological phase of life that should be managed with the minimum of interference and a valuable opportunity to invest in the future health of mother and child. The evident advantages of a non-medicalized pregnancy are counterbalanced by the risk of missing the opportunity to diagnose non-symptomatic diseases, which can affect both pregnancy and the long-term health of the mother and offspring, of which CKD is probably the most frequent and clinically relevant one. Pregnancy complications are closely associated with the future development of chronic cardiovascular and kidney diseases



Output							
	n	1296	1552	1613	1613	1754	1788
	%	64.8	77.6	80.7	80.7	87.7	89.4
	€/p	111	254	151	151	282	192

FIGURE 2: Cost per new diagnosis, assuming a production cost of serum creatinine of 0.20 euros per test.

[42–46], while CKD is associated with a higher risk of pregnancy complications [1–3] and preeclampsia has recently been associated with a high prevalence of CKD, as much as about 20%, found in post-natal assessment [29, 47–49]. While postnatal screening for kidney diseases is increasingly being suggested at least for patients who experience pregnancy complications [22, 29, 46–50], some data suggest that baseline kidney function, even in the normal range, may be associated with pregnancy outcomes, as pregnancy represents a sort of 'stress test' that can predict the development of future maternal diseases [51–54].

Adding serum creatinine to the pregnancy tests would make it possible to detect kidney diseases characterized by a reduction in kidney function that are not accompanied by proteinuria and would increase our understanding of the relationship between kidney function and pregnancy outcomes. The test is standardized and relatively inexpensive, is widely available and can easily be added to the set of laboratory analyses that are routinely prescribed [28]. The expenditure of adding serum creatinine to the tests already performed during pregnancy (albeit with subtle differences) in most European countries would result in an increase in expenditure by the healthcare system of 0.20 euros (one test only) to 1 euro per pregnancy (5 tests), in the settings in which the basic controls in pregnancy are free of charge (production costs: Table 1).

Due to the high heterogeneity of the assumptions derived from the literature, regarding both clinical elements that may be modulated by genetics and lifestyle, such as the prevalence of CKD and incidence of miscarriages and social ones, including adherence to prescribed controls and voluntary pregnancy terminations, or the prevalence of CKD unawareness, we decided to build a very simple flexible model, based on a decision tree, that would be adaptable to other settings (Figures 1 and 5).

With the current assumptions, the cost per detected case of CKD stages 3b–5 ranges from about 100 to almost 300 euros and the best performance (about 90% diagnostic yield) is intermediate (about 200 euros per detected case) and combines one test before, one during and one after pregnancy (Table 2, Figure 3). The modular calculator allows changing the parameters, adapting them to different contexts. For instance, reducing the adherence to one test in pregnancy from 30 to 20% in miscarriages, and from 50 to 20% after pregnancy, would result, in scenario 1, in a decrease in diagnostic yield from 64.8 to 62.1% and from 80.7 to 79.2% in scenario 3; likewise, reducing the post-pregnancy tests from 50 to 25% would decrease the performance of scenario 6 from 89.4 to 85%.

This analysis, which has the strength of novelty, may help us determine the feasibility of a policy of universal screening in pregnancy, increasingly advocated at least by the nephrology community, but has several limits that should be addressed in future studies.

First, many of the assumptions derived from the literature are based on imprecise estimates and indirect evaluations. Secondly, we considered that the detected cases would not have been detected solely by urinalysis, acknowledging the importance of non-proteinuric CKD. The actual prevalence of such cases is unknown and only the systematic introduction of kidney function tests in pregnancy will make it possible to compare the diagnostic yield of urinalysis and serum creatinine assessments. This is also why we choose a conservative figure of 50% of known CKD; this figure can be modulated in the calculator, thus varying the cost per case detected (online calculator).

Thirdly, we considered that compliance would be stable during pregnancy, while it may vary across trimesters, and we considered that all pregnancy losses would occur in the first trimester. Furthermore, we did not consider over-diagnosis, due to laboratory variability and the inclusion of cases with pregnancy-related AKI. However, the model is based on the assumption that serum creatinine is dosed on the occasion of the usual tests performed in pregnancy and these are usually avoided in the presence of diseases potentially causing AKI, when extra tests are usually prescribed, including kidney function assessment. Furthermore, the 90% detection rate, employed in our model, is based upon empiric reasoning and is not validated in different contexts.

The advantages of early diagnosis of kidney disease are intuitive, at least for nephrologists, and a cost of about 200 euros for identifying a relatively advanced (stage 3b–5) and probably evolutive kidney disease seems reasonable, taking into account the extremely high costs of advanced CKD management or dialysis, estimated at about 75 000 euros per patient per year in the study setting, a figure that is not substantially different from what is recorded in most western countries [55, 56]. An indirect advantage of this approach is that it may contribute to establish normal creatinine values for pregnancy in different trimesters and to better understanding of the trajectories of CKD in pregnancy, by performing

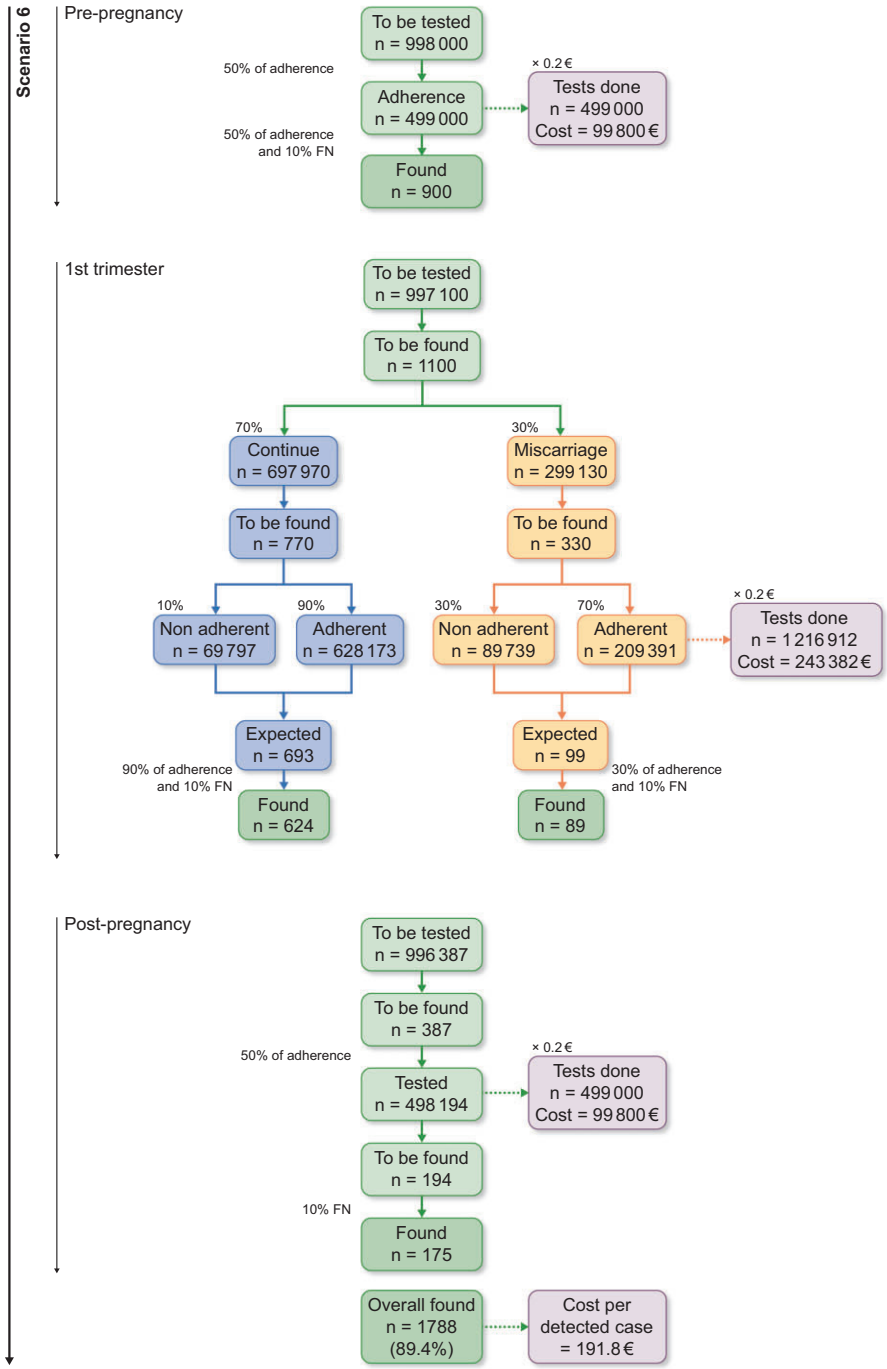


FIGURE 3: Flow chart displaying the diagnostic yield at each step in the most favourable scenario 6, combining tests before, during and after pregnancy.

systematic measurements in case of kidney function reduction at the screening test. Standardization of serum creatinine measurement will, of course, be necessary.

We acknowledge, however, that we do not know the long-term impact of early CKD diagnoses. We know that not all kidney diseases are alike and that many of them do not progress over long periods of time [57, 58]. Furthermore, even if the indications of several nephrology societies, including ours, are in favour of early identification of all cases of CKD, no randomized study has assessed the advantages of such a demanding policy [59–61]. We do, however, know the effects of a late CKD diagnosis, which involves lost opportunities for individuals and for society [62–64].

This study suggests the feasibility of early CKD diagnosis in pregnancy and offers cost estimates for further discussion. Only prospective studies that systematically test serum creatinine in pregnancy can actually clarify the cost-effectiveness of the inclusion of this test in the pregnancy work-up and in improving the short- and long-term health of the mother and her offspring.

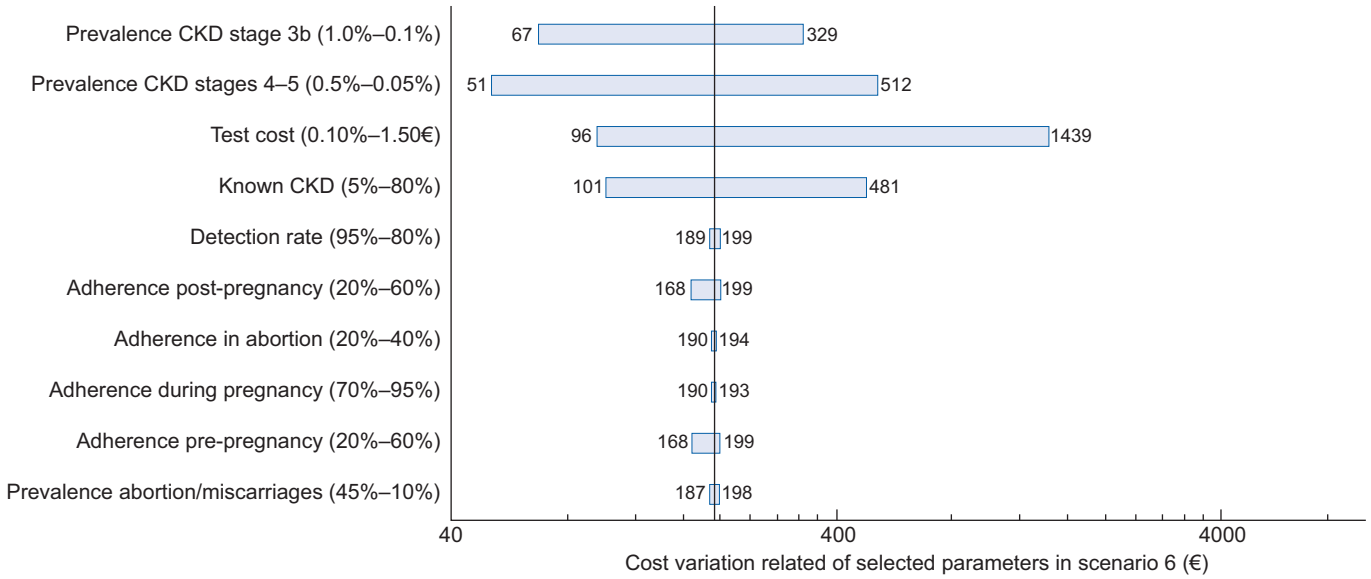


FIGURE 4: Sensitivity analysis for scenario 6. CKD, chronic kidney disease. The input parameters are reported in Table 1.

Input		
Population	1 000 000	Default: 1 000 000
Cost	0.2	Default: 0.20 €
CKD prevalence: Stage 3 Stages 4–5	 0.00267 0.001333333	 Default: 0.002666667 (i.e., 0.267%) Default: 0.001333333 (i.e., 0.133%)
Unknown CKD	0.2	Default: 0.5 (i.e., 50% of the cases)
Rates of: Miscarriage Continuing	 0.3 0.7	 Default: 0.3 (i.e., 30% of the cases)
Adherence in: Miscarriage Continuing Pre-pregnancy Post-pregnancy Test detection rate	 0.3 0.9 0.5 0.5 0.9	 Default: 0.3 (i.e., 30% of miscarriages) Default: 0.9 (i.e., 90% of continuing pregnancy) Default: 0.5 (i.e., 50% of the cases) Default: 0.5 (i.e., 50% of the cases) Default: 0.9 (i.e., 90% of the tests performed)

FIGURE 5: Input page of the downloadable calculator.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We thank Susan Finnel for her careful language editing.

AUTHORS' CONTRIBUTIONS

Research idea and study design: G.B.P.; data acquisition: A.C., M.C., R.A., B.M., G.C., E.V.; data analysis/interpretation: A.C., M.T., G.B.P.; statistical analysis: A.C.; drafting: G.B.P.; final version: all authors. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for their own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

FUNDING

No funding was received for this study; the Centre Hospitalier Le Mans supported editing and publishing expenses.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest for any of the authors. The results presented in this paper have not been published previously in whole or in part.

APPENDIX

The group members of Kidney and Pregnancy Study Group of the Italian Society of Nephrology are Domenico Santoro, Gabriella Moroni, Linda Gammaro, Giuseppe Gernone and Bianca Covella.

REFERENCES

1. Zhang JJ, Ma XX, Hao L *et al.* A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. *Clin J Am Soc Nephrol* 2015; 10: 1964–1978
2. Nevis IF, Reitsma A, Dominic A *et al.* Pregnancy outcomes in women with chronic kidney disease: a systematic review. *Clin J Am Soc Nephrol* 2011; 6: 2587–2598
3. Piccoli GB, Cabiddu G, Attini R *et al.* Risk of adverse pregnancy outcomes in women with CKD. *J Am Soc Nephrol* 2015; 26: 2011–2022
4. Istituto Superiore di Sanità. *Gravidanza fisiologica [Physiological pregnancy]*. https://www.salute.gov.it/imgs/C_17_pubblicazioni_1436_allegato.pdf (10 October 2021, date last accessed)
5. Haute Autorité de Santé. Suivi et orientation des femmes enceintes en fonction des situations à risque identifiées [Follow-up and management of pregnant women according to identified risks]. https://www.has-sante.fr/portail/jcms/c_547976/fr/suivi-et-orientation-des-femmes-enceintes-en-fonction-des-situations-a-risque-identifiees (10 October 2021, date last accessed)
6. American College of Obstetricians and Gynecologists. Routine tests during pregnancy. https://www.acog.org/womens-health/faqs/routine-tests-during-pregnancy (10 October 2021, date last accessed)
7. National Institute for Health and Care Excellence. *Antenatal care. NICE guideline [NG201]*. https://www.nice.org.uk/guidance/ng201 (10 October 2021, date last accessed)
8. National Institute for Health and Care Excellence. Chronic kidney disease: assessment and management. NICE guideline [NG203]. https://www.nice.org.uk/guidance/ng203/chapter/Recommendations#investigations-for-chronic-kidney-disease (10 October 2021, date last accessed)
9. Ogunwole SM, Chen X, Mitta S *et al.* Interconception care for primary care providers: consensus recommendations on preconception and postpartum management of reproductive-age patients with medical comorbidities. *Mayo Clin Proc Innov Qual Outcomes* 2021; 5: 872–890
10. Brown MA, Holt JL, Mangos GJ *et al.* Microscopic hematuria in pregnancy: relevance to pregnancy outcome. *Am J Kidney Dis* 2005; 45: 667–673
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: 1–150
12. National Kidney Foundation. National Kidney Foundation, American Society for Clinical Pathology, leading laboratories and clinical laboratory societies unite to diagnose chronic kidney disease. https://www.kidney.org/news/national-kidney-foundation-american-society-clinical-pathology-leading-laboratories-and (10 October 2021, date last accessed)
13. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA* 2019; 322: 1294–1304
14. Chu CD, Chen MH, McCulloch CE *et al.* Patient awareness of CKD: a systematic review and meta-analysis of patient-oriented questions and study setting. *Kidney Med* 2021; 3: 576–585.e571
15. Koeda Y, Tanaka F, Segawa T *et al.* Comparison between urine albumin-to-creatinine ratio and urine protein dipstick testing for prevalence and ability to predict the risk for chronic kidney disease in the general population (Iwate-KENCO study): a prospective community-based cohort study. *BMC Nephrol* 2016; 17: 46
16. Chu CD, McCulloch CE, Banerjee T *et al.* CKD awareness among US adults by future risk of kidney failure. *Am J Kidney Dis* 2020; 76: 174–183
17. Tummalapalli SL, Vittinghoff E, Crews DC *et al.* Chronic kidney disease awareness and longitudinal health outcomes: Results from the REasons for Geographic and Racial Differences in Stroke Study. *Am J Nephrol* 2020; 51: 463–472
18. Piccoli GB, Zakharova E, Attini R *et al.* Pregnancy in chronic kidney disease: need for higher awareness. A pragmatic review focused on what could be improved in the different CKD stages and phases. *J Clin Med* 2018; 7: 415
19. Luyckx VA, Cherney DZI, Bello AK. Preventing CKD in developed countries. *Kidney Int Rep* 2020; 5: 263–277
20. Kaul A, Bhaduaria D, Pradhan M *et al.* Pregnancy check point for diagnosis of CKD in developing countries. *J Obstet Gynaecol India* 2018; 68: 440–446
21. Ibarra-Hernandez M, Alcantar-Vallin ML, Soto-Cruz A *et al.* Challenges in managing pregnancy in underserved women with chronic kidney disease. *Am J Nephrol* 2019; 49: 386–396
22. Piccoli GB, Alrukhaimi M, Liu ZH *et al.* Women and kidney disease: reflections on World Kidney Day 2018. *Kidney Int* 2018; 93: 278–283
23. Harel Z, McArthur E, Hladunewich M *et al.* Serum creatinine levels before, during, and after pregnancy. *JAMA* 2019; 321: 205–207
24. Wiles K, Bramham K, Seed PT *et al.* Serum creatinine in pregnancy: a systematic review. *Kidney Int Rep* 2019; 4: 408–419
25. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008; 336: 211–215
26. Hill NR, Fatoba ST, Oke JL *et al.* Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016; 11: e0158765
27. Webster P, Lightstone L, McKay DB *et al.* Pregnancy in chronic kidney disease and kidney transplantation. *Kidney Int* 2017; 91: 1047–1056
28. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! *Nephron* 2017; 136: 302–308
29. Cabiddu G, Mannucci C, Fois A *et al.* Preeclampsia is a valuable opportunity to diagnose chronic kidney disease: a multicentre study. *Nephrol Dial Transplant* 2021. doi: 10.1093/ndt/gfab225.
30. Chepulis L, Paul R, Lewis-Hills E *et al.* Ethnic inequities in screening for diabetes in pregnancy in New Zealand-adherence to national guidelines. *N Z Med J* 2020; 133: 106–113
31. Rodin D, Silow-Carroll S, Cross-Barnet C *et al.* Strategies to promote postpartum visit attendance among medicaid participants. *J Womens Health (Larchmt)* 2019; 28: 1246–1253
32. Wilcox A, Levi EE, Garrett JM. Predictors of non-attendance to the postpartum follow-up visit. *Matern Child Health J* 2016; 20: 22–27
33. Linnakaari R, Helle N, Mentula M *et al.* Trends in the incidence, rate and treatment of miscarriage-nationwide register-study in Finland, 1998-2016. *Hum Reprod* 2019; 34: 2120–2128
34. Wang X, Chen C, Wang L *et al.* Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril* 2003; 79: 577–584
35. World Healt Organization. *Preventing unsafe abortion*. https://www.who.int/news-room/fact-sheets/detail/preventing-unsafe-abortion (10 October 2021, date last accessed)
36. Plebani M. Errors in clinical laboratories or errors in laboratory medicine? *Clin Chem Lab Med* 2006; 44: 750–759
37. Gruenberg JM, Stein TA, Karger AB. Determining the utility of creatinine delta checks: a large retrospective analysis. *Clin Biochem* 2018; 53: 139–142
38. Drummond MF, O'Brien B, Stoddart GL *et al.* Cost benefit analysis. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford University Press: New York, 1997; 209–212
39. Iannazzo S. The health-economic models: practical aspects and management of uncertainty. *Farmeconomia. Health economics and therapeutic pathways* 2006; 7: 239–245
40. Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. *BMJ* 1999; 319: 635–638
41. Weinstein MC, O'Brien B, Hornberger J *et al.* Principles of good practice for decision analytic modeling in health-care evaluation: report of the

ISPOR task force on good research practices—modeling studies. *Value Health* 2003; 6: 9–17
42. Theilen LH. Pregnancy as a window to future health: what next? *BJOG* 2020; 127: 1498
43. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort. *Circulation* 2015; 132: 1234–1242
44. Cain MA, Salemi JL, Tanner JP *et al.* Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes. *Am J Obstet Gynecol* 2016; 215: 484.e481–484.e414
45. Barrett PM, McCarthy FP, Kublickiene K *et al.* Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. *JAMA Netw Open* 2020; 3: e1920964
46. Covella B, Vinturache AE, Cabiddu G *et al.* A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia. *Kidney Int* 2019; 96: 711–727
47. Filali Khattabi Z, Biolcati M, Fois A *et al.* Chronic kidney disease in preeclamptic patients: not found unless searched for-Is a nephrology evaluation useful after an episode of preeclampsia? *J Nephrol* 2019; 32: 977–987
48. Kountouris E, Clark K, Kay P *et al.* Postnatal assessment for renal dysfunction in women with hypertensive disorders of pregnancy: a prospective observational study. *J Nephrol* 2021; 34: 1641–1649
49. Kattah AG, Scantlebury DC, Agarwal S *et al.* Preeclampsia and ESRD: the role of shared risk factors. *Am J Kidney Dis* 2017; 69: 498–505
50. Piccoli GB, Cabiddu G, Castellino S *et al.* A best practice position statement on the role of the nephrologist in the prevention and follow-up of preeclampsia: the Italian study group on kidney and pregnancy. *J Nephrol* 2017; 30: 307–317
51. Bjornstad P, Cherney DZI. Kidney function can predict pregnancy outcomes. *Clin J Am Soc Nephrol* 2017; 12: 1029–1031
52. Park S, Lee SM, Park JS *et al.* Midterm eGFR and adverse pregnancy outcomes: the clinical significance of gestational hyperfiltration. *Clin J Am Soc Nephrol* 2017; 12: 1048–1056
53. Koratala A, Kazory A. Renal functional reserve and pregnancy outcomes. *Kidney Int* 2017; 92: 768
54. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP *et al.* Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis. *Pregnancy Hypertens* 2018; 12: 169–173
55. Vanholder R, Lameire N, Annemans L *et al.* Cost of renal replacement: how to help as many as possible while keeping expenses reasonable? *Nephrol Dial Transplant* 2016; 31: 1251–1261
56. Vanholder R, Davenport A, Hannedouche T *et al.* Reimbursement of dialysis: a comparison of seven countries. *J Am Soc Nephrol* 2012; 23: 1291–1298
57. Li L, Astor BC, Lewis J *et al.* Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis* 2012; 59: 504–512
58. Lambers Heerspink HJ, Tighiouart H, Sang Y *et al.* GFR decline and subsequent risk of established kidney outcomes: a meta-analysis of 37 randomized controlled trials. *Am J Kidney Dis* 2014; 64: 860–866
59. Black C, Sharma P, Scotland G *et al.* Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess* 2010; 14: 1–184
60. Smart NA, Dieberg G, Ladhani M *et al.* Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014; CD007333
61. Heaf J, Heiro M, Petersons A *et al.* Choice of dialysis modality among patients initiating dialysis: results of the Peridialysis study. *Clin Kidney J* 2021; 14: 2064–2074
62. Chen YY, Chen L, Huang JW *et al.* Effects of early frequent nephrology care on emergency department visits among patients with end-stage renal disease. *Int J Environ Res Public Health* 2019; 16: 1158
63. de Jager DJ, Voormolen N, Krediet RT *et al.* Association between time of referral and survival in the first year of dialysis in diabetics and the elderly. *Nephrol Dial Transplant* 2011; 26: 652–658
64. Jungers P. Late referral: loss of chance for the patient, loss of money for society. *Nephrol Dial Transplant* 2002; 17: 371–375

Received: 4.11.2021; Editorial decision: 21.1.2022