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MEETING REPORT

CKD and Pregnancy Outcomes in Africa: A Narrative Review

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Chronic kidney disease (CKD) is associated with adverse maternal and fetal outcomes and is reported to affect up to 3% of women of reproductive age in high-income countries, but estimated prevalence may be as much as 50% higher in low and middle-income countries (LMICs). All pregnancy complications occur much more frequently in women in LMICs compared with those in high-income countries. Given the anticipated high prevalence of CKD in women of reproductive age and high rates of maternal and fetal adverse events in Africa, we sought to explore the association between CKD and pregnancy outcomes in this setting through a narrative review of the literature. This review demonstrates the paucity of data in this area and highlights the systemic barriers that exist in many African countries that prevent robust management of noncommunicable diseases such as CKD during a woman's reproductive life. This evidence gap highlights the need for further research, starting by sampling normal ranges of serum creatinine concentrations in pregnant and nonpregnant women of reproductive age in the diverse populations of Africa, estimating prevalence of CKD, and understanding associated pregnancy outcomes. Research should then focus on pragmatic interventions that may improve outcomes for women and their infants.

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CKD is reported to affect up to 3% of women of reproductive age in high-income countries,[S1] but estimated prevalence is at least 50% higher in LMICs with even higher rates reported for women with more advanced disease.[S2,S3] For example, a recent systematic review of the prevalence of CKD in LMICs[S2] reported estimates of CKD Stages 1 to 5 affecting 6.6% (95% confidence interval [CI], 6.2%–7.3%) and 9.0% (95% CI, 8.6%–9.7%) in women aged 20 to 29 years and 30 to 39 years, respectively. More severe disease (Stages 3–5) was estimated to affect 2.0% (95% CI, 1.4%–3.3%) and 3.1% (95% CI, 2.1%–5.1%) in the 2 age categories, respectively. Although successful pregnancy is possible for women with renal disease, CKD has been associated with an increased risk of adverse pregnancy outcomes when compared with the healthy pregnant population.[S4–S9]

All pregnancy complications are several-fold higher in women in LMICs compared with those in high-income countries. Globally, each year it is estimated that pregnancy hypertension, fetal growth restriction, and stillbirth unrelated to intrapartum events are associated with 46,000 maternal deaths and 2.5 million fetal, neonatal, and infant deaths.[S10] More than 99% of these deaths occur in LMICs and more than half in sub-Saharan Africa.[S10]

Given the anticipated high prevalence of CKD in women of reproductive age and high rates of maternal and fetal adverse events in Africa, we sought to explore the impact of CKD on pregnancy outcomes in this setting through narrative review of the literature. This review discusses the impact of CKD on pregnancy outcomes in African countries.

Estimates of CKD in Pregnancy in Africa

To inform our narrative review we undertook a systematic search of the literature from 2005 (when the definition for CKD was launched)[1] for CKD (defined

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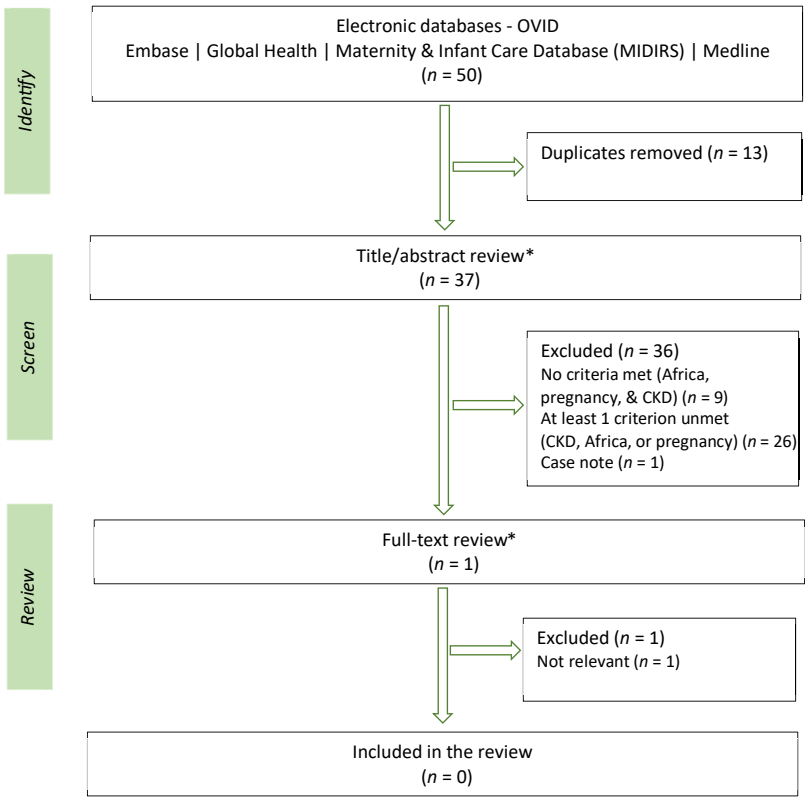

Figure 1. Study selection process for chronic kidney disease (CKD) in pregnancy in Africa. *Assessed independently by 2 authors (DCA and SPM); any discrepancies were discussed and resolved through consultation with a third review author (KB).

according to Kidney Disease: Improving Global Outcomes guidelines)[2] in pregnancy in Africa (Figure 1 and Supplementary Table S1). Only 1 paper remained for full-text review, a retrospective review of pregnancy outcomes after renal transplantation in Egypt from 2005,[3] which because of its study design was unable to contribute to meaningful discourse, as no appropriate denominator was measured to be able to infer incidence or prevalence.

Our search of the literature demonstrated no data describing the prevalence and impact of CKD on pregnancy outcomes in Africa. Similarly, other reviews report that there is a paucity of robust data describing the epidemiology of CKD generally in the adult population in Africa.[4,5] Other studies have focused on CKD prevalence in high-risk groups, such as people living with HIV and diabetes, whereas others report rates of CKD diagnosis in varying heterogeneous groups such as rural and urban communities, and very few stratify for age and sex, giving little scope to infer prevalence in women of reproductive age. Quality of studies is compromised by variable laboratory techniques in the measurement of creatinine levels to define CKD, lack of follow-up creatinine tests, and inconsistent use of equations to estimate glomerular filtration and correction for ethnicity. Despite these challenges, there is a general consensus that CKD is highly prevalent and likely an escalating disease in sub-Saharan Africa, driven by a triple burden of early life stressors, infectious conditions associated with poverty, and now noncommunicable diseases of hypertension and diabetes as the continent undergoes a great nutritional and demographic transition associated with rapid urbanisation.[6]

Estimates of CKD in Women of Reproductive Age in Africa

It may be possible to make some broad inferences from current literature about prevalence of CKD in women of reproductive age. Worldwide, evidence suggests that prevalence of CKD in women aged 20 to 39 years is higher in low-income countries compared with high-income countries.[S2] In a systematic review of CKD prevalence studies in Africa,[4] 6 of 29 studies reported prevalence with stratification by age, with CKD (estimated glomerular filtration rate <60 ml/min) rates in 18- to 40-year-olds ranging from 3.4% to 7.2% in urban and semi-urban Tanzania,[7] 6.4% to 7.6% in urban and rural Northern Tanzania,[8,9] 16% in urban Uganda,[10] 0.8% to 6.1% in Northern Egypt,[11] and 8.7% to 18.6% in urban Kinshasa.[12] All of these studies showed higher rates of CKD in men, although meta-analysis[S2] suggested a higher prevalence in women aged 30 to 39 years.

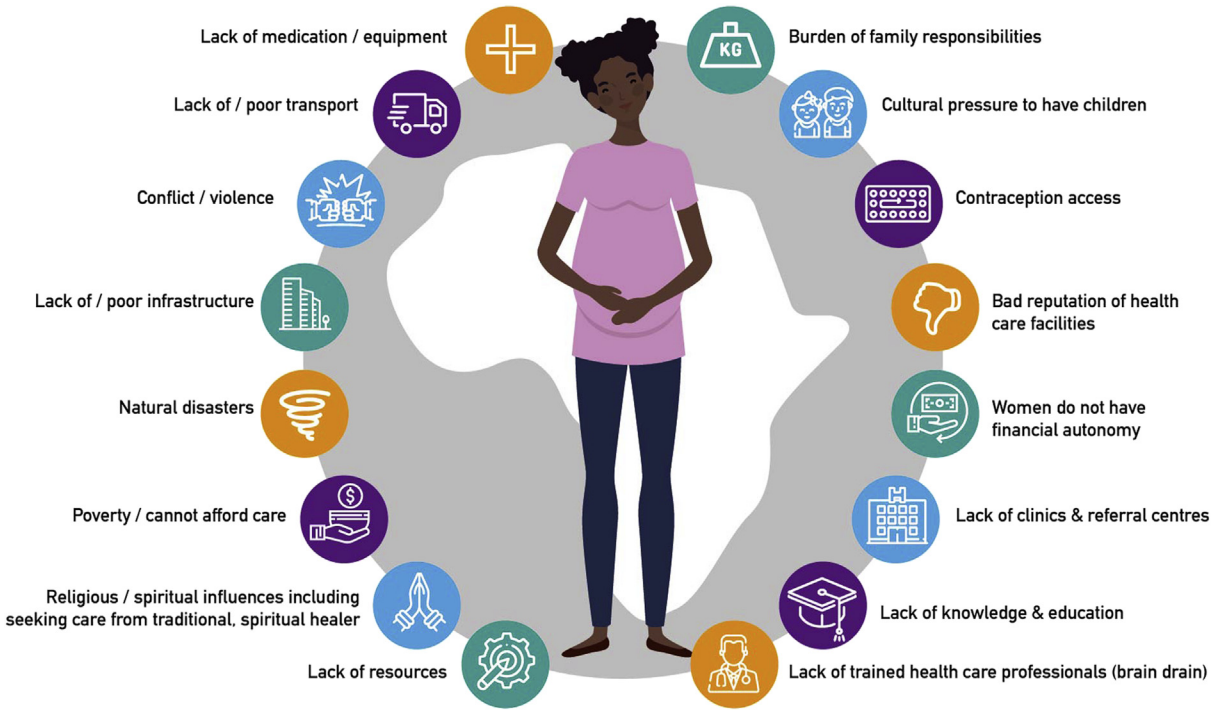

Figure 2. Influencing factors on pregnant women with chronic kidney disease in Africa.

Population studies of hypertension, which may be a cause or consequence of CKD, also give some insight into possible CKD prevalence in women of reproductive age. A large population study of almost 30,000 adults in Malawi[13] estimated a prevalence of hypertension in women aged 18 to 39 years of approximately 2% to 12%, with significantly higher rates in urban compared with rural communities. An epidemiological survey in Uganda[14] reported a prevalence of hypertension of 12.8% to 22.9% in 18- to 39-year-olds. Similarly, a 4-country pooled analysis of cross-sectional studies of different population groups in Uganda, Tanzania, Nigeria, and South Africa[15] suggested rates of 18.6% to 27.2% in this age group. These studies are limited by variation in devices used and operating procedures, diurnal and contextual fluctuations in blood pressure readings, and use of arbitrary cutoffs. Nevertheless, it seems a substantial proportion of women of reproductive age in sub-Saharan Africa may have risk factors for renal disease that may then be revealed under the physiological stress of pregnancy.

Pregnancy Outcomes in Women With CKD

Data from high-income settings indicate that maternal complications, including preeclampsia, requirement for cesarean delivery, and pregnancy loss (including miscarriage and stillbirth), are significantly more common in women with CKD compared with healthy pregnant women, reported in population studies,[S6] cohort studies,[S5] and meta-analyses.[S7] Women with CKD also have significantly higher rates of fetal complications, such as preterm delivery, low birth weight, and perinatal mortality compared with healthy pregnant women.[16,S4] It is possible that undiagnosed CKD may contribute to high rates of adverse pregnancy outcomes in pregnant women in Africa; however, our review has shown that accurate assessment of the impact of CKD on pregnancy outcomes in African countries has not been undertaken.

Pregnancy-Associated Progression of CKD

Although CKD may increase the risk of poor pregnancy outcomes, the physiological demand of pregnancy itself also may lead to permanent deterioration in renal function in women with underlying kidney disease. The risk of progression of disease appears to be low for women with mild renal impairment (CKD stages 1 and 2), low-level proteinuria, and absent or well-controlled hypertension,[S7] but for women with more advanced renal impairment, risk of disease progression during and after pregnancy appears to be substantial, with up to a third having more than 25% loss in kidney function or requirement for renal replacement therapy.[S5,S8,S9] Furthermore, there is the potential for further adverse pregnancy outcomes and renal injury with subsequent pregnancies, which is likely to impact substantially on women with CKD and their families.

Pregnancy-Associated Acute Kidney Injury

In addition to progression of disease from normal physiological demand, pregnancy is a particular risk factor for acute kidney injury (AKI). In Africa,

pregnancy-associated AKI is reported as the most common cause of severe AKI requiring dialysis in young women.[17–19] The threat is posed via various mechanisms, which will depend on local factors such as legality of abortion, exposure to infectious diseases such as malaria and HIV, infrastructure of obstetric care, and local contact with nephrotoxins (see Figure 2).

It is proposed that a greater proportion of pregnancy-related AKI in low-income settings is caused by prerenal mechanisms such as sepsis and obstetric hemorrhage with high risk of long-term kidney damage from cortical necrosis. Although in the high-income setting preeclampsia and hypertensive disorders account for a greater proportion of pregnancy-associated AKI,[20] these factors appear to also be of increasing importance in low-income settings. For example, a recent study in South Africa reported that 17% of women with preeclampsia had AKI, one-third of surviving women had not recovered renal function at discharge, of whom half had no further renal function testing.[16] Similarly, a study in Malawi[21] described preeclampsia as the commonest cause of AKI in high-risk maternity admissions to a tertiary center.

AKI may either cause or contribute to CKD, with preexisting CKD increasing risk of further acute insults,[22] but has not yet been reported in African pregnancy cohorts. An example case from Kenya is presented in Table 1. Interventions to reduce incidence or severity of pregnancy-associated AKI are unlikely to be etiology-specific, but part of the complex bundle of interventions that aim to improve overall antenatal and peripartum care. Additional benefits in women with CKD include reduction of risk of progression of disease, thus, awareness of CKD during pregnancy could enable targeted care to those with greatest need.

Africa-Specific Challenges in Management of CKD in Women of Childbearing Age

Women in sub-Saharan Africa with CKD face many challenges, which are outlined in Figure 2, and demonstrated in an example case from Kenya that is presented in Table 1. First, as is the case with many noncommunicable diseases in Africa, a woman may be unaware of her CKD until it is at advanced stages. The health infrastructure of many African countries is organized to manage acute illnesses such as pneumonia, malaria, and diarrhea, with less focus on the longitudinal care of chronic disease. The relatively new phenomenon of long-term survival with HIV means that the continent is seeing the development of its first dedicated chronic disease care-streams,[23] but these often remain externally funded by vertical projects that tackle single conditions, such as HIV, in isolation. Similar-quality services are yet to be seen for chronic cardiovascular and metabolic disorders, with lack of trained staff in noncommunicable disease care, and lack of basic bedside and laboratory equipment to measure blood pressure and creatinine.[24–26]

Second, even if mild to moderate renal impairment was diagnosed, the costs of treatment to prevent deterioration are currently likely to be prohibitive in many countries. Antihypertensive and antidiabetic medications are often unavailable in the public sector and must be bought privately. For example, a month's treatment with metformin costs approximately 1 week's wage for the average government worker in Kenya.[27] Successful management of CKD often requires several pharmacological and dietary interventions, and any costs for an asymptomatic condition are not likely to be prioritized.

Table 1. Example case (hypothetical patient based on similar real-world scenarios) of pregnancy in Kenya complicated by chronic kidney disease and acute kidney injury

Case example

A 39-year-old woman was referred to nephrology services on day 2 postpartum for consideration of dialysis due to oliguria, widespread edema, with raised creatinine and hyponatremia (see table following the text). She had hypertension in 2 previous pregnancies, and in this pregnancy was found to have severe hypertension (184/102 mm Hg) at 38 weeks of gestation. Her only medical history was a prolonged hospital admission for severe malaria as a teenager. She reported taking aspirin intermittently during her pregnancy but had attended few antenatal appointments with her midwife due to costs of travel to the antenatal clinic. Her blood pressure had been recorded as 128/82 at 24 weeks and 139/88 at 32 weeks, but no other recordings were available, and urine dipsticks had been out of stock. She had an emergency induction after the diagnosis of preeclampsia was established and had a vaginal delivery of a live but low-birthweight neonate (2.37 kg, fifth centile of weight for gestational age) who was admitted to the special care infant unit at 6 hours after birth due to poor feeding. Delivery was complicated by a large postpartum hemorrhage from a cervical tear. Her blood pressure was controlled with oral labetalol 200 mg 3 times per day. She was given rectal diclofenac 75 mg twice daily for pelvic pain, and furosemide 40 mg twice daily due to the widespread edema. After assessment in the nephrology department, she was offered hemodialysis due to persistent hyperkalemia but opted for conservative management because of the inability to raise funds from extended family. Fortunately, her renal function partially recovered and she diuresed spontaneously. She was offered contraception on discharge but said she would first need to discuss with her husband at home. She was discharged at 14 days postpartum and repeat blood tests at 6 weeks postpartum suggested a diagnosis of chronic kidney disease. She was unable to breastfeed her infant and was required to buy formula at personal cost.

Parameter	Admission	Day 2 postpartum	Discharge at 14 d postpartum	6 wk postpartum
Creatinine (μmol/l)	280	588	292	181
Urea (mmol/l)	16	29	12	10
Sodium (mmol/l)	130	122	132	138
Hemoglobin (g/dl)	10.2	9.2	7.8	8.1
Platelets (cell $\times 10^6$/ml)	20	22	104	144

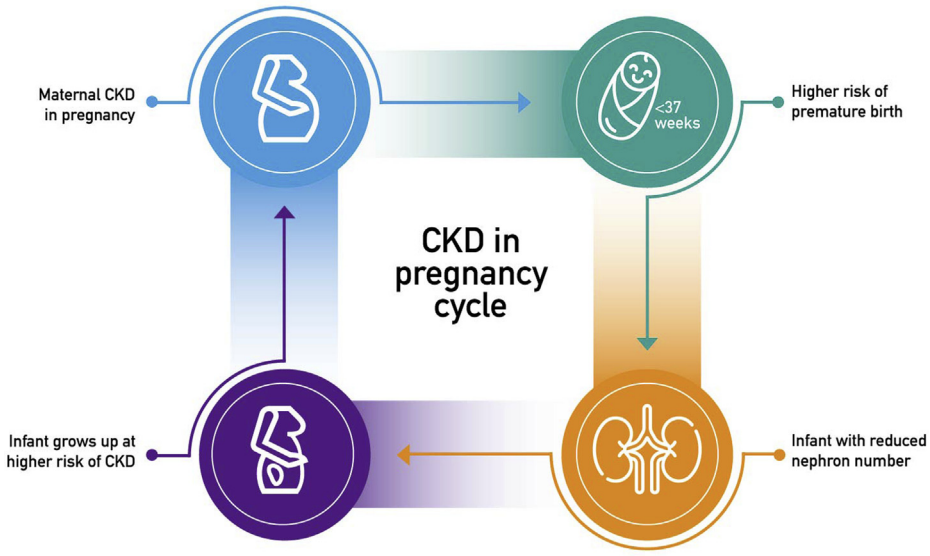

Figure 3. Chronic kidney disease (CKD) in the pregnancy cycle.

Third, the development of end-stage renal failure and associated costs have major health implications in many African countries. There is a huge unmet need for dialysis across the continent, with only 1.5% of those requiring renal replacement therapy ever receiving it.[28] As typical examples; Uganda, which has a population of almost 43 million people, has 3 nephrologists and 25 hemodialysis machines.[29] In Ghana, the situation is slightly better, with 8 nephrologists and 103 dialysis machines serving a population of 23 million. However, distribution is markedly skewed, with more than half of regions having no access to dialysis, and most resources concentrated around the capital in the greater Accra region.[30] Costs per dialysis session are typically approximately $100, and as in most countries in sub-Saharan Africa, transplant services are not available and would incur costs of approximately $50,000 abroad,[31] which is unaffordable to most (mean gross domestic product per capita in Uganda is less than $2 per day,[32] and in Ghana $6 per day).[33] In countries where dialysis may be offered free by the government, such as Malawi, an economic debate concerning provision of that service clearly exists.[34,35] Even where dialysis is offered, quality of life and chances of long-term survival remain poor.[36]

These deficiencies in provision of CKD care must also be taken in the context of cultural barriers that women face accessing health care in sub-Saharan Africa.[37] Women are less likely to be educated about the importance of chronic disease management, and less likely to have the financial autonomy to pay for appropriate treatment. Many populations in sub-Saharan Africa also commonly seek care from traditional or spiritual practitioners, which may lead to delay in management, mismanagement, or even detrimental management with nephrotoxic agents (see Figure 2).

Contraception Choices in Africa

Women in sub-Saharan Africa may be unable to access prepregnancy counseling and contraception. There remains a large unmet need for contraception in sub-Saharan Africa in the general population,[38,39] and it is very likely that this includes those with CKD. There is considerable variation in gender inequality across the continent, with many women having minimal choice on pregnancy timing. The total number of pregnancies is likely to affect progression of CKD, from physiological stress and risk of AKI. This may be particularly important in older women; although many consider age

Table 2. Proposed priorities for improving pregnancy outcomes for women with CKD in Africa

Prepregnancy strategy	Antenatal strategy	Postpartum strategy
Appropriate contraception	Targeted antenatal care including aspirin and blood pressure control in pregnancy	Maternal monitoring and blood pressure control after delivery
CKD optimization and blood pressure control	Enhanced antenatal monitoring	Appropriate contraception
Patient education about pregnancy risk with CKD	Recommended delivery in setting with appropriate support	CKD optimization and blood pressure control
Avoidance of nephrotoxins	Avoidance of nephrotoxins	Avoidance of nephrotoxins

CKD, chronic kidney disease.

of having children to be lower in Africa due to the high adolescent pregnancy rate, the mean age of having a child is actually 1.5 years higher compared with the rest of the world, at 29.1 versus 27.6 years,[40] and incidence of CKD in older women is likely to be higher. Access to contraception for older multiparous women could contribute to reducing the rate of pregnancy-associated CKD progression.

Infant Risk of CKD

In addition to the real-time associations of AKI, CKD, and peripartum complications, there is mounting evidence that poor pregnancy outcomes affect long-term cardiovascular health in the child.[41,42] Kidney development is completed in the last stages of pregnancy, with premature birth and placental insufficiency thought to disrupt this process, leading to a low nephron endowment in those infants born premature and/or small-for-gestational age.[43,44] It is assumed that this anatomic nephron deficit contributes to increased long-term cardiovascular risk, although this has not been proven conclusively with the inability to count nephrons *in vivo* and need for very long cohort studies, with many confounding genetic and environmental variables. This intergenerational transfer of cardiovascular and CKD risk between a mother and her infant highlight the need to improving understanding kidney health of pregnant women in Africa (Figure 3).

Clinical Implications and Future Research

The paucity of data revealed by this review yields great potential for future research. The first step is to describe normal ranges of serum creatinine levels in pregnant and nonpregnant women of reproductive age, in populations that represent the heterogeneity of the continent. Large cohort studies such as those initiated by the PRECISE network,[45] which will follow women in The Gambia, Kenya, and Mozambique, offer such opportunity. Advances in point-of-care tests for underlying kidney disease, including capillary blood creatinine concentration and proteinuria, mean that real-time identification at first antenatal booking may be possible, potentially aligned with testing for other underlying medical conditions, such as diabetes and anaemia, in addition to standard point-of-care tests for HIV and syphilis.

Antenatal diagnosis of chronic disease could facilitate triage into appropriate care-streams, ranging from dedicated antenatal clinics to basic advice regarding location of delivery and postpartum care, depending on local resources. In addition, cheap pharmacological interventions that are known to reduce risk of poor pregnancy outcomes in women with CKD, such as aspirin,[46,47] could have considerable benefit in low-income settings. In addition to intervention strategies during pregnancy, the identification of CKD would allow for targeted contraception advice to those at risk of progression of underlying disease. This would potentially garner benefit for women, their families, and the societies in which they live, long after her reproductive life is over. These, along with other strategies, are summarized in Table 2.

Conclusion

Little is known about CKD prevalence in women of reproductive age in African countries, but it is likely to be substantially higher than in high-income countries. Pregnancy is a potential time to diagnose asymptomatic chronic disease, offering the opportunity to reduce poor pregnancy outcomes, progression of disease in later life, and perhaps even transfer of cardiovascular and renal risk to future generations. Interventions should not be delivered in isolation, but as part of wider packages of antenatal care provision that incorporate pregnancy as part of a woman's entire life course. Such advances in maternal care serve women, their families, and their communities, and act as a fulcrum for wider socioeconomic development.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Search strategy for CKD in pregnancy in Africa.
Supplementary References.

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