# KDIGO Controversies Conference on Women and Kidney Health
# - Public Review Comments -

**As of January 6, 2023**
**Industry comments are highlighted in blue**

**Sreedhar Mandayam (University of Texas MD Anderson Cancer Center):**
Very curious to examine the role of ApoL1 genotype on CKD in women, pregnancy complications and risk for CKD in children with ApoL1 heterozygosity.

**Darshana Dadhania (Weill Cornell Medicine):**
Dear KDIGO Team,

This is a great initiative and very important questions have been proposed. Just to introduce myself, I am a transplant nephrologist at an academic center in US. As you may agree, all kidney transplant recipients have CKD but CKD post kidney transplantation may be very different compared to CKD alone. Several factors impact the long-term success of the kidney transplant in women - Sensitization status and primary glomerular disease as the cause of ESKD. I think these issues should be outlined and evaluated in Group 1 or added as a separate entity. The management of HRT and Bone Health are understudied in post-transplant population, including persistent tertiary HyperPTH management.

Second, Living Donors are more likely to be women. This disparity and the optimizing the kidney health of these living donors should also be addressed in this important conference.

Thank you,
Darshana

**Jose Weisinger (Florida International University):**
I think that you should also consider in the conference differences in care between women with CKD, especially those on dialysis, as compared to healthy women, in terms of gynecological follow up, mammography screening, and post-menopausal care, including osteoporosis.

**Rolando Claure-Del Granado (Hospital Obrero No 2):**
Analyzed if different healthcare systems have the structured so that all have equal opportunities to have optimal kidney health care for women.

Monitor gender and sex specific epidemiologic patterns and determinants of kidney health and kidney disease.

**Natasha Dave (Strive Health):**
Wonderful topic and so incredibly needed. Would recommend if sexual dysfunction to be added as a topic prior to pregnancy and perhaps discussion on treatment of menopause.

**Sylvia Stracke (University Medicine Greifswald):**
Do women really have a lower GFR than men/ less nephrons/ smaller kidneys - to me this does not make sense because women have a higher life expectancy? But if so, why are there no sex specific reference levels for CKD? If CKD starts at 60 ml/ min, then nearly all women over 70 years will have CKD and are prone to be overtreated - meanwhile it maybe a normal kidney health status and no disease.

- Overtreatment: ACEI and ARBs do not work as well for women than for men, the same is true for ASS after myocardial infarction. I am missing research on sex and gender specific dosages and drug efficacy.

- We need to rethink guidelines - there is a knowledge gap nearly everywhere. This needs to be mentioned - as an example: hypertension starts at 140/90 for all, but for women, 130/80 already leads to higher cardiovascular morbidity and mortality.

- Postmenopausal women need an extra focus as the missing of estrogen leads to an increase in cardiovascular morbidity. I have never read a guideline addressing postmenopausal women.

- Why is also animal research mostly done on male animals and even in vitro studies on male cells (or sex unknown)?

- Why aren't there more female leaders in Nephrology?

- Can I take part in this KDIGO initiative?

Best wishes, Sylvia

**Minika Staszkow (Medical University of Warsaw):**
Dialysis Kidney transplantation Glomerulonephritis

**Marius Miglinas (Vilnius University):**
Protection strategies of reproductive health in lupus female patients on intensive and/or long-term immunosuppression should be discussed.

**Deepak Sharma (Ketav Kalp Healthcare**):
Well considered points

**Lesley Inker (Tufts Medical Center):**
The very limited mention of menopause and potential treatments is notable. CKD is a disease of aging. The role of menopause is important. This is hard to study and will have limited data but a clear discussion of the issues from the conference would be helpful.

**Kunitoshi Iseki (Nakamura Clinic):**
Certainly, the scope of this CC is much more important both for patients and physicians. Gender difference in CKD, in particular end-stage renal disease, is one of the clinical questions. We have published papers such as Kidney Int 63: 1468-1474, 2003, Kidney Int 74(4), 415-417, 2008. We hypothesize that high incidence of premature birth and high prevalence of metabolic syndrome in men.

Recently we published a study on preterm birth in our district (Yoshino Kinjyo et al. Risk factors of preterm birth in Okinawa Prefecture, the southernmost island prefecture in Japan. Maternal and Child Health Journal 2022 Nov 9). Also, we are conducting studies on gender difference in ESRD patients with the collaboration of the Japanese Society for Dialysis Therapy; TSUBASA PROJECT). The aim of this project is also to promote women physicians working at the dialysis clinic.

**Lynne Roberts (St George Hospital):**
This is a great document, well done! I have a couple of comments/suggestions:

Page 1, first paragraph -consider changing 'kidney disease patients' to 'patients with kidney disease'

Page 11, point 15 - The latest ISSHP guidelines (Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 27 (2022) 148–169) recommend that the terms severe and mild preeclampsia should not be used

Pre-eclampsia should not be classified as 'mild' or 'severe' in an ongoing pregnancy. Better to say something like 'more severe symptoms', or 'more symptoms' instead of mild or severe.

**María Carlota Gonzalez Bedat (SLANH/Latin American Dialysis & Renal Transplantation Registry/Uruguayan Dialysis Registry):**
In Uruguay, the National Renal Healthcare Program (NRHP) has entered 27207 patients at 12/31/2021, 58% male. The Uruguayan Dialysis Registry (UDR) report an incidence of male = 63% and a prevalence of male = 60%. The UDR is mandatory and have a completeness of 100%.

The access to the KRT is universal in the country. There are no NRHP with the development of the Uruguayan in the other Latin American countries and the quality of the KRT registries is very inequal between them. 12 of 20 countries report an incidence of male= 50-60% and a prevalence of male = 50-70%. (The Latin American Dialysis & Renal Transplantation Registry in not mandatory).

We are now focused in study the accessibility of women to KRT in Latin America, since we think that there might be disparities and inequities that give account of the gross differences. We are preparing the second ""Gender in Nephrology Symposium" where we will show the data.

**Tarik Sqalli (Hassan II University Hospital):**
I propose adding a question on the place of the gender issue in scientific guidelines.

**Urmila Anandh (Amrita Hospitals):**
The scope of work should review literature from LMICs (however scarce) and suggest recommendations appropriate for the socio-economic status of the patient concerned. Can be considered as practice points.

In the section in pregnancy, the group should look into clinical situations where termination of pregnancy should be considered. This should encompass all trimesters of pregnancy.

Nutrition of the pregnant mother with CKD should have recommendations appropriate to the cultural and dietary patterns of not just developing world but rest of the world.

In every issue deliberated, the social determinants should be addressed and recommendations should take into consideration these factors.

Finally, the work group should be inclusive and diverse and have representations of nephrologists from all corners of the world.

**Vincent Lee (University of Sydney):**
Congratulations for organising this very important KDIGO conference. The scope of work is very comprehensive.

Suggestions:

What are the specific issues in the approach to managing women undergoing surgery (e.g. prediction of adverse outcomes)

Considerations for drug therapy (especially ACE inhibitors) during breastfeeding, particularly women with hypertension.

Genetic diseases e.g. X-linked conditions and their inheritance, especially screening.

**Edwina Brown (Imperial College Healthcare NHS Trust):**
I am not sure where delivery of dialysis round needs of women and issues to be raised in shared decision making about dialysis modality fit in. For example:

1. Women with young children often have to get up at night - barrier to APD but not CAPD. Can be barrier to PD in countries with high use of APD e.g. US

2. Presence of PD catheter / fistula on body image and sexual appeal

3. Discussions about PD or HD regime to fit in with sexual activity (exhausted after HD?) presence of catheter a deterrent

**GHADA ANKAWI (KING ABDULAZIZ UNIVERSITY):**
THANK YOU FOR GIVING ME THE OPPORTUNITY TO SHARE MY FEEDBACK

THREE POINTS I WOULD SUGGEST CONSIDERING:
1. PREGNANCY TESTING IN DIALYSIS-DEPENDENT PATIENTS AND HOW ESRD AFFECTS ITS INTERPRETATION.
2. INDICATIONS TO START DIALYSIS IN PREGNANT WOMEN, BOTH FOR AKI AND CKD THAT IS PROGRESSING ""DURING PREGNANCY"".
3. BREASTFEEDING IN THE DIFFERENT SCENARIOS (TRANSPLANT RECEPIENTS, DIALYSIS PATIENTS ETC).

**Tess Harris (PKD International):**
I welcome the conference. Will you be considering reproductive options, especially genetics related, eg counselling, access to pre-implantation genetic testing, terminations arising from genetic conditions in the fetus?

**Christopher Chan (University Health Network):**
Dialysis dose and women fertility was mentioned in the text. The practice of family planning with patients on dialysis is now preferred in Toronto.

In terms of research questions: There is a need to compare pregnancy outcomes between kidney transplantation and intensive hemodialysis.  Planned versus unplanned pregnancy outcomes (despite the use of intensive HD).

**Dominique Martin (Deakin University):**
The scope of work looks generally great and I appreciate I have a biased perspective, so I don't expect that every ethical aspect of the various topics can be addressed - so many of the current questions listed have ethical implications! I'm also conscious that lack of research on the normative aspects of many of these issues means that there is very little evidence on which to draw when considering the following types of questions...

- how do/might (perceived) ethical concerns influence inclusion or exclusion of people who identify as female or non-binary gender in clinical trials and other research about CKD? (e.g., do concerns about privacy inhibit collection of data about gender, or do concerns about conducting research with individuals or groups deemed to be ""vulnerable"" discourage inclusion?) How might such ethical concerns or considerations be addressed to promote equity and inclusion?

-how do existing medical ethics guidelines/frameworks and/or understanding of ""core"" ethical principles support decision-making about reproductive care for people with CKD? (e.g., does current/established guidance effectively support clinicians and patients grappling with complex decision-making about risks and benefits of pregnancy?) How might ethical guidance be improved? More specifically, what underpins paternalism in care for women with CKD of child-bearing age, and how can paternalism be avoided? Should genetic testing be routinely offered to prospective parents with inheritable kidney disease?

- of lesser value, but certainly controversial in some places is the question of whether/to what extent public healthcare services should provide access to assisted reproductive treatment for people with complex needs due to kidney failure esp those with transplants.
I'm very much looking forward to participating in the meeting.

**Titia Lely (Wilhelmina Children's Hospital (WKZ) - Utrecht University):**
Dear colleagues,

We would like to congratulate you on the work already done and wish you all the best with this huge effort. As a clinical geneticist specialized in nephrogenetics (ass prof dr. Albertien van Eerde, UMC Utrecht) & a fetal-maternal medicine specialist in the Netherlands with a successful renal obstetrics clinic since several years (ass prof dr. Titia Lely, UMC Utrecht) & MD, PhD-candidate in Obstetrics & Genetics (drs. Margriet Gosselink), we have recently contributed to the Dutch guideline on pregnancy & kidney disease (also recently published in KI Reports 2022).1

Yet with our experience in both ERKNET, ERA-EDTA, working experience abroad and scientific collaborations on kidney disease & pregnancy, we are also aware of practices outside the Netherlands. We hope we are helping you with the conference meeting by writing down our suggestions and thoughts on the Scope of Work for this conference. We are happy to discuss this in more detail.

In general

- We would like to emphasize the need for investigating pregnancy outcomes per etiology of kidney disease. This links to breakout group 2.4. Established risk factors on which pre-pregnancy counselling in women with CKD is currently based are pre-pregnancy CKD-stage, chronic hypertension and proteinuria. Most studies on pregnancy in women with CKD are based on heterogeneous cohorts that include patients with a variety of etiologies of kidney disease without differentiating outcomes per specific etiology of kidney disease or based on general distinctions. The differences in reported pregnancy outcomes of these cohorts might be explained by the modifying effect of etiology of kidney disease on pregnancy outcomes. To facilitate the clinician in providing individualized counseling for patients, we believe more information should come available on disease-specific pregnancy outcomes and effect of pregnancy on long-term kidney function.
- We would like to emphasize the need for (qualitative) patient-centered research with patients also participating in these studies. For example, the past year, we have conducted a focus group study among patients with ADPKD and their clinicians regarding their perspectives and wishes on family planning, according to the three reproductive stages 'pre-pregnancy, during pregnancy & after pregnancy'. These results will be shared upcoming year with the inclusion of a comprehensive guidance 'tool' for these patients regarding family planning, based on their own preferences.

This initiative and this type of research matches with the last ADPKD KDIGO research agenda where the need was outed for the 'Production of a comprehensive family planning guide, with research on outcomes. Role of peer-to-peer support networks and youth counselors for children and adolescents.2 We think this is not only the case for ADPKD, but for CKD in general as well: the patients' voice should be represented in research as well.

Per breakout group

Breakout group 1: Sex Differences in Prevalence, Incidence and Outcomes in CKD

1. Are there sex ander gender differences in the presentation, diagnosis and access to care for CKD?

a. As stated in the recent Dutch Practice Guideline on pregnancy (wish) in CKD, we advise clinicians to assess at an early stage whether patients with CKD and a wish to conceive may have a hereditary kidney disease.

b. In our experience, among clinicians there can be the assumption that X-linked diseases primarily affect men (in Alport Syndrome for example). However, as described by Savige et al (CJASN 2016), more women than men get affected by X-linked AS. Women get underdiagnosed because female relatives of affected men are not systematically screened in adult nephrology

practice.3 It is wise to be aware of the possible risks for women in an X-linked family and to see them before pregnancy for proper counselling.

c. Furthermore, we would like to add that the other way around, men with CKD are often overlooked when planning preconception counselling visits. Improvements can be made by providing pre-pregnancy counseling for men, that should also cover information on teratogenicity of certain medication. When men are affected by hereditary kidney diseases, they should also be provided with information on reproductive options regarding family planning (such as pre-implantation genetic testing and other options).

Breakout group 2: Reproductive Care of Women with CKD Not on Dialysis Therapy

2. What are the best methods for detecting CKD in the pre-conception phase or pregnant women worldwide?

a. We believe that women without an established diagnosis of kidney disease, but who are at high risk for monogenic kidney diseases, because of these diseases occurring in the family, would benefit from a preconception check of the Protein-Creatinine Ratio (PCR) and a blood pressure measurement. This because if blood pressure is high, hypertension can be treated with better pregnancy outcomes as a consequence. Furthermore, accurate risk stratification of these women and individualized pre-pregnancy counseling can take place.

a. What impact does the specific underlying nephropathy have on pregnancy outcome in patients with CKD?

a. Highly relevant subject. Please read in the general part above for more explanation on this topic.

6. What is the optimal counselling strategy of women with CKD planning or starting a pregnancy, and how can it be adapted to different settings?

a. As explained in the Dutch Guideline of Pregnancy & CKD, please consider the advice of multidisciplinary pre-pregnancy counselling, preferably performed by a nephrologist and a maternal-fetal medicine specialist. Also, it is important to consider the possibility of the kidney disease being a hereditary disorder, and not to forget genetic counseling in the pre-pregnancy advice in women and men with CKD.4 Furthermore, one of the key aspects we found in our focus groups with ADPKD patients, was the need for timely information, because the process of family planning can be time consuming and women are experiencing time pressure due to a ‘biological deadline’ existing of both maternal age and the risk of deterioration of kidney function in the future.

8. What is the optimal medical (nephrology, obstetric, neonatal medicine) follow-up of patients with CKD?

a. Elaborated on this in the Dutch Guideline of Pregnancy & CKD

10. What biomarkers are helpful for the follow-up of pregnant women with CKD?

a. As shown by Wiles et al and Bramham et al, PlGF can be a valuable biomarker in establishing the diagnosis of pre-eclampsia during pregnancy.5 6 We believe that the next step is to conduct intervention studies to investigate whether these biomarkers also have added clinical value, next to an already existing close-monitoring policy (as is existing in the Netherlands for example) and whether costs of such biomarkers weigh up against benefits.

17. What are indications for the follow-up of the children?

a. Please consider children that are at high risk (50% or more) of developing a hereditary kidney disease, to be followed up with blood pressure measurements and proteinuria screening. We would like to refer to the article by van Gimpel et al7. As stated by Kashtan CE et al8, ACE-inhibition is proven to be renal-protective and slows down disease progression.

Breakout Group 3: Reproductive Care of Women on Dialysis Therapy or with Kidney Transplant

1. What are the key trends in birth rates for individuals on kidney replacement therapy across countries?
a. As stated in recent PARTOUT-network publication9, per decennium, the incidence of pregnancies after KT are increasing. In the last decennium, between 2010 and 2017, there were approximately 13 pregnancies after KT/year in the Netherlands.
2. What are the expected pregnancy outcomes and which are the main differences between countries?
b. Please consider taking into account our recent publication in Kidney International in 2022 and Transplantation 2021, in which we showed that pregnancy outcomes after KT in the Netherlands are relatively good and that there is little influence of pregnancy on long-term kidney function.9 10
3. What is the optimal counseling strategy of women on kidney replacement therapy planning or starting a pregnancy, and how can it be adapted to different settings?
a. Please consider the advice following from the Dutch Guideline of Pregnancy & CKD1 would advise multidisciplinary counselling, preferably performed by a nephrologist and a maternal-fetal medicine specialist. Also, it is important to consider the possibility of the kidney disease being a hereditary disorder, and not to forget genetic counseling in the pre-pregnancy advice in women and men with CKD4. Furthermore, one of the key aspects we found in our focus group with ADPKD patients, was the need for timely information, because the process of family planning can be time consuming and women are experiencing a lot of time pressure due to a 'biological deadline' existing of both maternal age and the risk of deterioration of kidney function in the future.
4. What are the key clinical and health system factors that determine pregnancy and maternal kidney outcomes, and how do these differ between countries?
a. Please consider the outcomes of our recent study In the Netherlands on pregnancy & KT9, in which we saw that most important predictors for adverse pregnancy outcomes were prepregnancy kidney function and amount of hemodynamic adaptation to pregnancy (blood pressure drop during pregnancy and SCr drop during pregnancy). Due to missing values, proteinuria could not be investigated as predictor for adverse outcomes. For long-term kidney function, most important factor was also prepregnancy kidney function, and we only saw marginal influence of pregnancy on long term kidney function10.
5. What is expected to change in the next decades?
a. As described very accurately in the editorial published with our PARTOUT-manuscript in Kidney International by Jesudason et al, over the years, we see a trend of higher incidences of pregnancies in women with less ideal pre-pregnancy situations than described in guidelines. This ensures ethical dilemmas in clinical practice around pregnancy advice, but also regarding assisting such pregnancies by providing fertility trajectories. We believe it would be interesting

to further look into this and to weigh these ethical aspects, and also to establish the pros and cons regarding these assisted pregnancies in future research.11

13. How should available biomarkers be incorporated into the clinical follow-up of women undergoing dialysis and transplant recipients?

a. As shown by Wiles et al and Bramham et al, 5 6 PlGF can be a valuable biomarker in establishing the diagnosis of pre-eclampsia during pregnancy. The next step is to conduct intervention studies to investigate whether these biomarkers also have added clinical value, next to an already existing close-monitoring policy (as is existing in the Netherlands for example) and whether costs of such biomarkers weigh up against benefits.

16. Which indications require follow-up of the children?

a. To add to this relevant question, please consider the option to discuss what kind of information would be relevant to collect. Also, on what type of information is a need regarding the children from women who got pregnant after kidney transplantation?

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**Liz Lightstone (Imperial College London):**
Will be attending the conference and am in group 2. There is quite a lot of overlap (unsurprisingly) between the 3 groups which focus on pregnancy but there are some inconsistencies.

Fertility assessment and treatment needs to be in Group 2 (it appears in group 3 but not group 2)

What about the children? This appears in different forms in groups 2,3 and 4 and I wonder if needs to be a topic addressed by all three groups together? I appreciate that makes some difficulties but if you want addressed by only one group then I'd suggest comes into group 2 as can mention impact of Preeclampsia, if on RRT but by far the largest group of children will be in group 2 women as it were.

No mention of risk of preeclampsia or acute on chronic KI in women with CKD and pregnancy in group 2. I appreciate how things have been split up but think there's going to be a lot of repetition between those 3 groups...

Birth control mentioned in group 2 but also very important in group 3 patients.

**Irma Tchokhonelidze (Tbilisi State Medical University, Georgia):**
One crucial element that could be integrated into the discussion is dry weight control in the third trimester of pregnant patients on dialysis, especially in those, with no residual kidney function. In the normal physiological state in the third trimester, the maternal plasma volume is expanded through a reduction in peripheral vascular resistance and retention of sodium and water. Although the sodium and water content in pregnant women undergoing hemodialysis can be controlled, peripheral vascular resistance depends on the physiology of the dialysis patient (increased arterial stiffness in CKD). Therefore, plasma volume expansion in pregnancy associated with an inadequate vasodilatory response may increase intraluminal pressure and further exacerbate hypervolemic status, provoking congestive heart failure. In addition, there is insufficient evidence to use bioelectrical impedance and lung ultrasound to identify

extravascular lung water (sonographic B-lines). The utility of these tools for targeting pregnant dialysis women's dry weight needs more consideration and research.

**Helen Yeh (Vice President, Global Medical Affairs CVRM, AstraZeneca):**

Dear Dr. Piccoli & Dr. Wyatt,

In response to KDIGO's invitation for feedback on the KDIGO Controversies Conference on Women and Kidney Health – Scope of Work, we would like to share our comments on behalf of AstraZeneca. The scope of work appears very comprehensive and would like to make the following suggestions:

| Section | Comment |
|---|---|
| **Breakout Group 1:** Sex Differences in Prevalence, Incidence, and Outcomes in CKD | We suggest a discussion of low diagnosis rates in early stages of CKD, with attention given to differences by sex and gender. While epidemiological studies have shown that CKD affects more women than men,[1] recent evidence suggests that women are less likely to receive a diagnosis, particularly in earlier stages.[2-6] These low diagnosis rates are despite an emerging consensus on the importance of early identification and intervention in CKD.[7] Addressing sex and gender disparities in screening and diagnosis of CKD will be essential to broadly improving outcomes.<br><br>We suggest that an explanation of the definitions of sex and gender and how this may affect eGFR calculations, the evidence for validation of these equations in these populations, and the validation of these equations after hormonal therapy/gender affirming surgery would be beneficial. Guidance on how to estimate GFR in these populations accurately so they can be treated correctly and dosed appropriately with medications would be helpful.<br><br>We suggest a discussion of differences by sex and gender of complications of CKD, including mortality rates, which while shown to be higher in males versus females, have risen faster in females with CKD over the last thirty years in some countries.[8] A related discussion on the implications for strategies to identify and intervene early would be helpful.<br><br>We also recommend increasing awareness on the effects of the premenopausal state and postmenopausal state[9] with regards to risks for hypertension, CKD, and CVD.<br>We suggest recommendations for a) healthcare systems and practices and<br>b) industry on increasing equity in gender and sex representation in studies in nephrology by incorporating evidence-based methods in |

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|---|---|
| | clinical trial design, recruitment, and increasing diversity of principal investigators and research staff[10] (which include improving opportunities for female nephrologists to lead as principal investigators in clinical trials).<br><br>We recommend discussion of the importance of standardized documentation in electronic health records to accurately identify sex, gender, and menopausal status so they can be captured accurately in clinical trials, and clear consistent definitions may aid accurate trial data collection. Differences in CV and mortality risk amongst these groups supports stratification.[9] |
| **Breakout Group 2:** Reproductive Care of Women with CKD Not on Dialysis Therapy | We suggest guidelines on CKD screening in women of reproductive age due to the prevalence of hypertension disorders of pregnancy, preeclampsia, gestational diabetes, and HELLP, which all increase the risk of CKD and CV disease. In addition, with the mortality rate of mothers postpartum being at an 'all-time' high in the USA, associated mortality risk awareness/education in patients with these diseases of pregnancy would be helpful.<br><br>We suggest postpartum recommendations on eGFR and UACR screening and monitoring for development of CKD and, in diagnosed CKD patients, frequency of eGFR monitoring so these patients can be treated earlier postpartum, to improve CKD outcomes. Lower rates of diagnosis in women versus men heightens the urgency to increase awareness.[2-6]<br><br>We recommend guidelines on safely prescribing recommended contraceptive methods in patients with risk factors for CKD, given that many women are prescribed oral contraceptives with a history of migraine with aura or hypertension (which may be undiagnosed) which increases their risk of stroke.[9] |
| **Breakout Group 3:** Reproductive Care of Women on Dialysis Therapy (Hemodialysis, Peritoneal Dialysis, Home Dialysis) or with Kidney Transplant | As the proposed content is very comprehensive, an additional suggestion would be to include the importance of patient-physician shared decision making, with emphasis on a non-judgmental approach to the patient's decision(s). |
| **Breakout Group 4:** Preeclampsia and AKI and Future Maternal-Child Health | As preeclampsia increases the risk of heart failure and CKD, follow up protocols that include monitoring for, and reducing risk of developing heart failure and CKD should be recommended. |

If you have any questions regarding the comments, please contact AstraZeneca Medical Information at 1-877-893-1510.

Yours sincerely,

Helen Yeh, PhD
Vice President, Global Medical Affairs Cardiovascular, Renal, Metabolic (CVRM)
AstraZeneca

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