
In the Name of God

Pregnancy and CKD.ESRD

INTRODUCTION

the number of women with chronic kidney disease (CKD) desiring a pregnancy is increasing.

First, it is because of the increasing maternal age with the inherent higher incidence ofCKD.

Second, it is because of improved treatment options and higher numbers of kidney transplantations leading to increased number of fertile women with CKD for whom pregnancy can be a safe option.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Preconception Counseling and Management

Sexual and Reproductive Health of Women With CKD

self-reported sexual dysfunction is common, affecting *30%-80%* of women with *CKD*.
women with *CKD* have lower sexual function with greater sexual distress compared with age-matched controls.
underlying reasons for these symptoms are alterations in hormonal milieu,comorbid depression/anxiety ,social and body image factors and medication side effects.
treatment of sexual dysfunction is available for men with CKD,but options are limited for women.

Pregnancy and CKD: Advances in Care and the Legacy of Dr Susan Hou, AJKD December 2021
Reproductive health and pregnancy in women with chronic kidney disease ,NATURE REVIEWS

Sexual and Reproductive Health of Women With CKD

fertility is also decreased in women with *CKD* because of alterations in the hypothalamic-pituitary-ovarian axis , in which low estradiol levels inhibit the pulsatile release of gonadotropin -releasing hormone and the midcycle surge of luteinizing hormone (LH) that leads to ovulation.

hyperprolactinemia,through diminished urinary excretion , can also suppress gonadotropin-releasing hormone.

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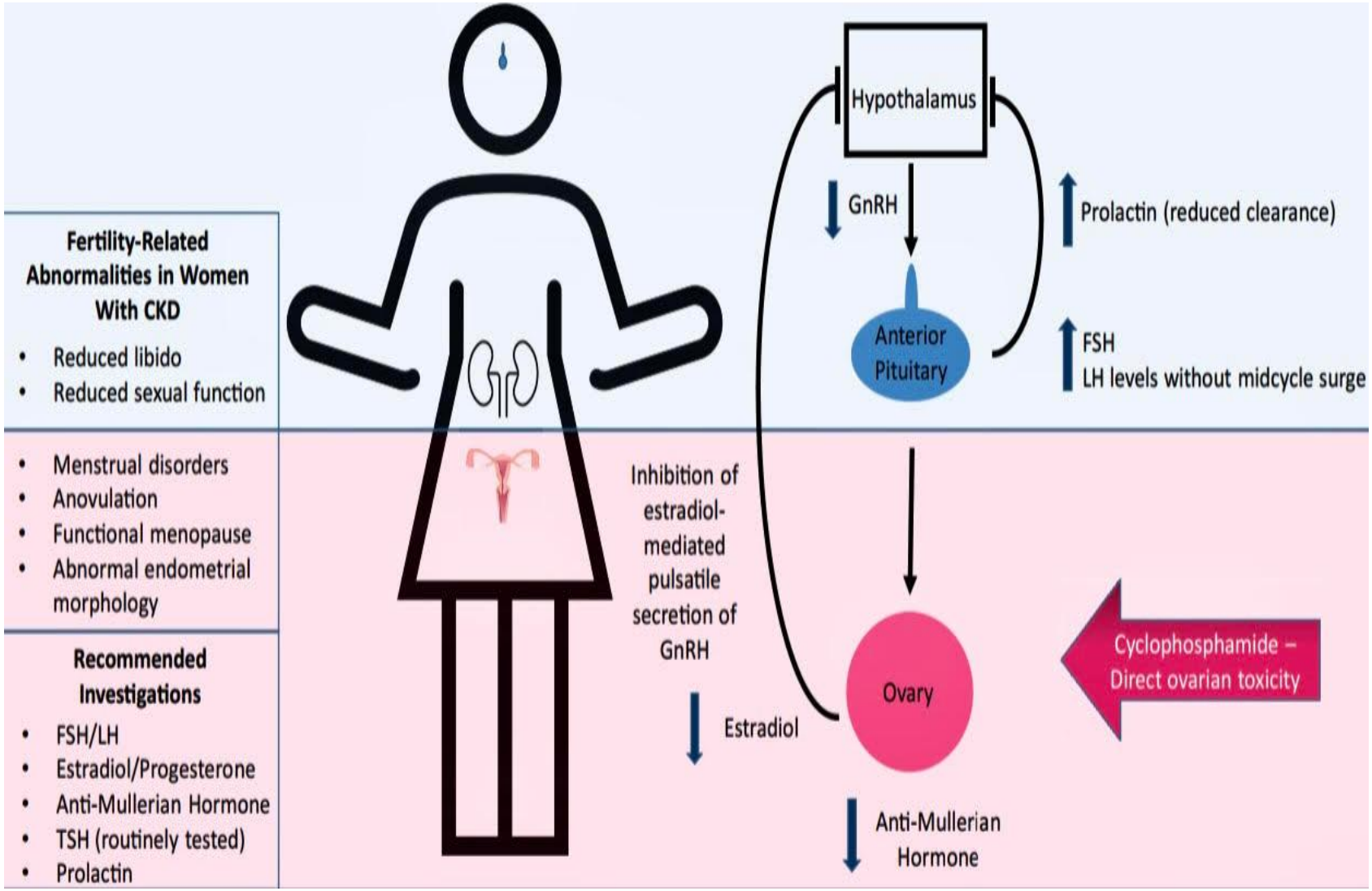

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Sexual and Reproductive Health of Women With CKD

however, the effects of all stages of CKD on the hypothalamic–pituitary–ovarian axis are thought to be reversible , and *normalization* of levels of gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)), prolactin and *oestrogen* is seen following renal transplantation.

Reproductive health and pregnancy in women with chronic kidney disease NATURE REVIEWS

Cyclophosphamide

cyclophosphamide treatment is associated with ovarian failure via induction of single-strand DNA breaks.

risk of sustained amenorrhea is dependent on the patient's *age* at the time of administration and the *dose administered.*

among women older than 31 years , 30% who Have received a total cumulative dose of 5 g/m2 Will experience sustained amenorrhea.

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Cyclophosphamide

Cryopreservation of oocytes or embryos can be undertaken before cyclophosphamide treatment is initiated.

Although natural- cycle oocyte retrieval and cryopreservation of ovarian tissue negate the need for ovarian stimulation, long-term fertility outcomes remain unclear in women with CKD.

Cyclophosphamide

In women with lupus , gonadotropin hormone – releasing analogues such as leuprolide decrease the frequency of persistent amenorrhea when administered with cyclophosphamide compared with cyclophosphamide alone.
It is ideal to administer leuprolide near the time of ovulation to the mid luteal phase; however, in the acuity of a flare, we often administer it concomitantly with the first dose of cyclophosphamide because prompt treatment is often critical.

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Maternal and Fetal Outcomes of Pregnancy in CKD

in women with an *Scr ≤1.4* mg/dL, decrements in kidney function associated with pregnancy were largely mild and reversible after Delivery.

In a subsequent analysis of 70 pregnancies among women with preexisting kidney disease and Scr of ≥1.4 mg/dL before pregnancy, 8% had a pregnancy-related decline in kidney function with recovery within 6 months post partum and *41%* had a *GFR decrease of ≥25%* of the baseline Value.

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Maternal and Fetal Outcomes of Pregnancy in CKD

the likelihood of adverse outcomes of preterm delivery,lower birth weight, need for higher-level neonatal care , and decline in maternal kidney function at more advanced CKD stages .

overall, the live birth rate is reported

at 86%-98% among women with CKD.

Increasing severity of prepregnancy proteinuria has been associated with increased odds of *preeclampsia* and *preterm delivery* in women with CKD.

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Maternal and Fetal Outcomes of Pregnancy in CKD

among those with chronic hypertension , the risk of delivery before 34 weeks increased from 20% to 40% if the gestational decrease in Scr was <10% of pre pregnancy

Chronic hypertension and *gestational Scr decrease of <10%* were the strongest predictors of a decrease in eGFR following pregnancy concentration.

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lupus nephritis

those with a flare within 6 months of conception are at significantly greater odds of a lupus flare during pregnancy and preeclampsia.
preterm birth occurred in 52% of pregnancies among women with active lupus nephritis, defined as proteinuria >0.5 g/d and/or active urine sediment before 20 weeks.low birth weight occurred in 46% of births to women with *lupus nephritis*, compared with 20% of womenwith *systemic lupus erythematosus without Nephritis*.

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lupus nephritis

Therefore, delayed conception until 6 months after lupus disease activity is recommended,and pre-pregnancy renal biopsy might be indicated to exclude active disease if *proteinuria is persistent*.

Hypocomplementemia at conception is independently associated with adverse pregnancy outcomes.

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Reproductive health and pregnancy in women with chronic kidney diseaseNATURE REVIEWS

lupus nephritis

For women with lupus nephritis and, active disease or proteinuria ,obstetrical antiphospholipid syndrom, prophylaxis against VTE using low-molecular-weight heparin should be considered.

Unless contraindicated , women with lupus nephritis should be offered ***low-dose aspirin for pre-eclampsia prophylaxis and hydroxychloroquine***

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Reproductive health and pregnancyin women with chronic kidney diseaseNATURE REVIEWS

lupus nephritis

Hydroxychloroquine is recommended in all pregnancies Affected by lupus and is associated with lower disease activity and prednisone dose at delivery.
as well as lower rates of *congenital heart block*
in children born to mothers who are positive for
anti-Ro or anti-La antibodies.

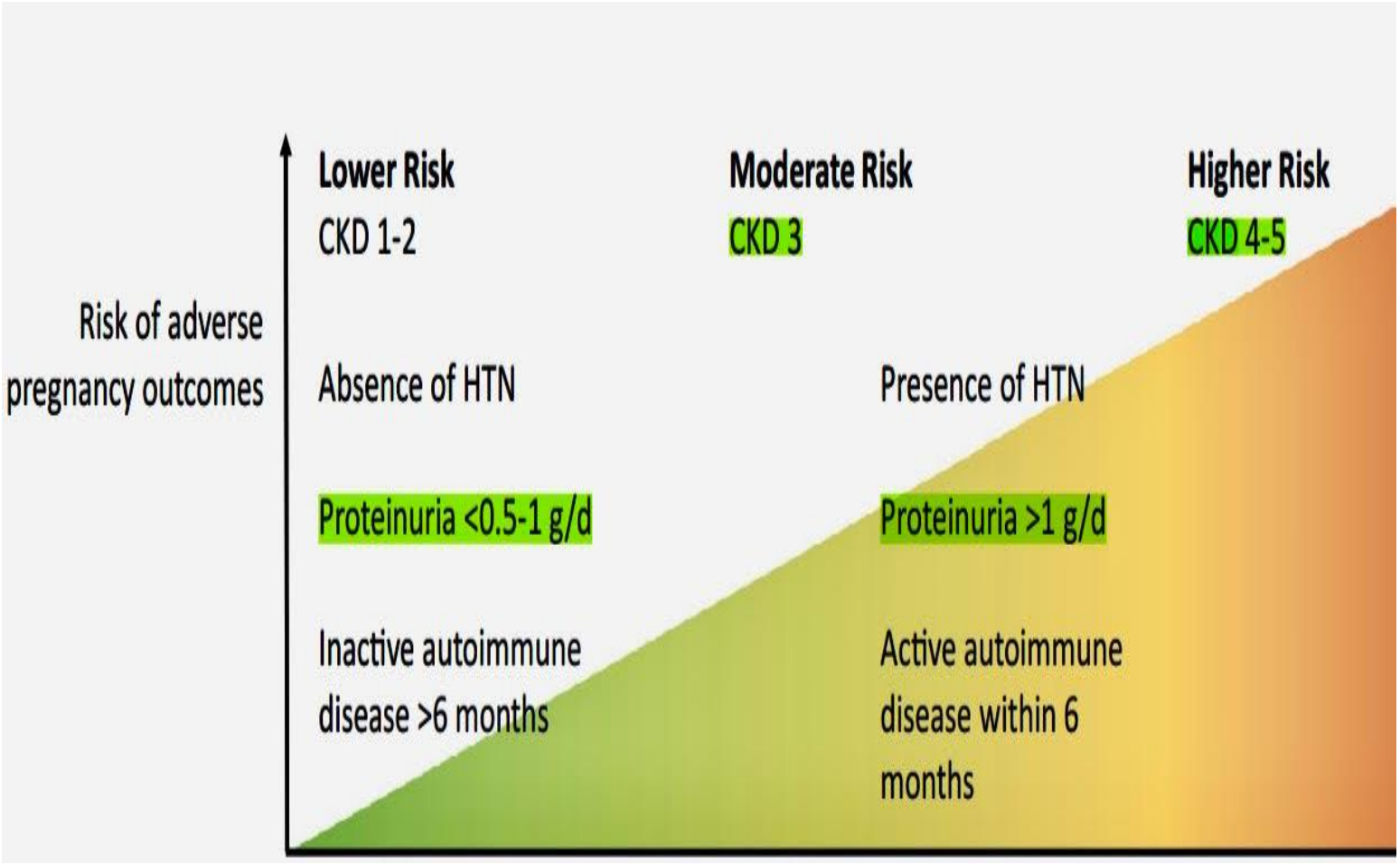
lupus nephritis

no guidelines exist in this regard (*Anticoagulation Therapy*) for *on-dialysis pregnancy*.

the standard practice includes low-dose ASA(usually *50 to 75* mg/day) in systemic lupus erythematosus(SLE) and in the presence of anti phospholipid antibodies *without previous thrombotic events*.

heparin is added in case of obstetric antiphospholipid syndrome(APS) or history of thrombotic events.

Unfractionated heparin is commonly used, but low-molecular-weight heparin has been shown to be safe and can also be used during the dialysis sessions.



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Preconception Counseling

Consultation with a CKD patient who wants to conceive, to be conducted by a nephrologist and maternal-fetal medicine specialist, should at least address the following aspects:

the possible effects of pregnancy on the underlying kidney disease and assessment of the risk of transient and/or permanent loss of renal function

timing of pregnancy.

specifically the risks of pregnancy complications such as hypertension , preeclampsia, intrauterine growth restriction,and(iatrogenic) premature birth

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD, Kidney International Reports (2022)

Preconception Counseling

the potential risk of teratogenic medication and, if possible, recommend discontinuation or switch to a safe alternative.
if the kidney disease is hereditary and carries an elevated risk of inheritance for future children, inquire if the couple would like to be informed about the various options for fulfilling their desire to have children without the genetic disorder.

general preconception advice, including stopping smoking, alcohol and/or drugs, weight reduction if *BMI >25 kg/m2,* and prophylactic use of daily *400 mcg of folic acid* before conception.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD, Kidney International Reports (2022)

Preconception Counseling

The disease of patients with CKDwith a desire to conceive should be stable ; if necessary, regulate their blood pressure (<130/80 mm Hg).

recommend that the patient takes *Acetylsalicylic acid* from the *twelfth week* of pregnancy (afterlast menstruation) to reduce the risk of hypertensive disorders during pregnancy.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD ,Kidney International Reports (2022)

Nephrological Treatment During Pregnancy

Diet Restrictions

Check sodium excretion in the 24-hour urine of pregnant patients with CKD(nondialysis (ND))and limit their daily salt intake to a maximumof 6 grams (=100mmol of sodium chloride equivalent to 2400 mg of sodium).

for pregnant women with CKD and (expected) High degree of sodium retention (manifesting as excessive weight gain combined with edema and/or hypertension), consider further limiting the daily salt intake to 3 grams(1200 mg sodium) during pregnancy.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKDKidney International Reports (2022)

Diet Restrictions

Continue or start pregnant patients with CKD for protein restriction on a diet of 0.8g/kg ideal weight per day throughout pregnancy .
and, therefore, *be reluctant* to increase protein intake in the second and third trimesters for dialysis patients.

for kidney patients with a (highly) advanced CKD stage (G3b-G5ND), consider prescribing a (stricter) protein-restricted diet of *less than 0.8 g/kg per day* during pregnancy to maintain their serum urea level at <17 mmol/l in order to prevent ***polyhydramnios, and a longer gestational age and a higher birth weight.***

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

Nephrological Treatment During Pregnancy

hypertention

When treating hypertension in patients with CKD and a desire to conceive, aim preconceptionally for *blood pressure <130/80 mmHg*,regardless of The proteinuria level.

During pregnancy, in patients with CKD (with or without albuminuria) who have:

not used antihypertensives before pregnancy or used antihypertensives before conseption, only initiate or intensify antihypertensive treatment, if their blood pressure measurements is *Higher than 140/90 mm Hg* on repeated,

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

hypertention

After birth, aim at a consistent blood Pressure_<130/80 mm Hg in patients with CKD.

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hypertention

Consider prescribing ***diuretics*** to patients With CKD with a desire to conceive only if:

their blood pressure does not reach the desired *target of <130/80 mm Hg* with the central alpha blocker,methyldopa,beta blockers or calcium channel blockers *due to (possible) sodium retention caused by their CKD*.

their *proteinuria is higher than 0.5 grams/day* in order to reduce the likelihood of sodium retention and associated hypertensive disorders during Pregnancy.

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hypertention

avoid starting *diuretics* if preeclampsia is suspected because *preeclampsia* is usually due to *excessive vasoconstriction* with Intravascular underfilling.

This may be aggravated by diuretics,with a negative effect on placental perfusion.

avoid *triamterene* and *aldosterone antagonists* (e.g . spironolactone) during pregnancy due to the risk of severe teratogenic effects.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

hypertention

Only recommend continuing *RAS inhibitors* in women with a desire to conceive if they are sufficiently aware of needing to stop taking the drug immediately if *2 consecutive pregnancy tests are positive* (*no later than 8 weeks of amenorrhea)* and have a strong indication, that is: diabetic nephropathy with at least moderate albuminuria (***A2, ACR> 3 mg/mmol***)
CKD and severely elevated albuminuria (***A3,ACR >30 mg/mmol***, corresponding to proteinuria >_0.5 g protein/24 hours or protein/ creatinine ratio >_0.5 g/10 mmol creatinine).

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

Group	Agent Safe in pregnancy	Considerations for the mother	Considerations for the child
Central acting sympathomimetic agents	Methyldopa	preconceptional amenorrhoea due to hyperprolactinemia -drowsiness, tiredness, depression -less effective in severe hypertension	Safe, also in long-term follow-up
Betablocking agents	In general Alfa and betablocking agent (labetalol)	careful in severe asthma and liver function disorder agent with most experience during pregnancy -can also be given IV -orthostatic hypotension, mainly with dosages >1200 mg/d	When used during delivery: small increased risk of hypoglycemia and very sporadic bradycardia. Consider monitoring postpartum,certainly with high dosages Possibly risk 1:500 of multicystic kidney dyplasia
Dihydropyridine calcium antagonists	limited evidence for safety in 1st trimester -safe in 2nd and 3rd trimester	very effective for treatment of preeclampsia in 2nd and 3rd trimester -frequently used tocolytic agent -be careful with high dosages in short time interval -edema-uterus atony	

Group	Agent Safe in pregnancy	Considerations for the mother	Considerations for the child
Loop and thiazide diuretics Preconceptional	safe when used preconceptionally -can be continued During pregnancy	Possible indications preconceptionally: -insufficient effect ofother agents or preconceptional - (glomerular) proteinuria>0.5 g/d Sideeffects:nausea/vomiting -hypokalemia،gout	No association with congenital defects
During pregnancy Hydrochlorothiazide furosemide	Start only with strict indication in 2nd half of Pregnancy Safe when started before coseption in case of fluid overload	Contraindication is suspicion of Preeclampsia. Possible indications: -fluid overload and/or nephrotic syndrome -heart failure	
Renin-angiotensin inhibitors	until 8 weeks amenorrhoea probably safe -from 8 weeks amenorrhoea teratogenic and fetotoxic	Consider continuation preconceptionally: 1. diabetic nephropathy with at least moderately increased albuminuria 2. chronic kidney disease with severely increased albuminuria or proteinuria >_0.5g protein/24h	Severe congenital defects and oligohydramnios because of fetal anuria

Preeclampsia:

Advances in Diagnosis and Treatment

Preeclampsia is a clinical syndrome characterized by new onset hypertension with *systolic BP >140* mm Hg or *diastolic BP ≥90* mm Hg *after 20 weeks*' gestation plus one or more manifestations of maternal organ dysfunction accompanied by *abnormal uteroplacental circulation*(fetal growth restriction).

although the clinical presentation occurs after 20 weeks' gestation,the pathogenesis of preeclampsia begins with abnormal placentation in the first trimester resulting in placental injury and ischemia,triggering a proinflammatory and antiangiogenic state.

Preeclampsia

an *increase* in the anti angiogenic marker *sFLT1* and a *decrease* in the angiogenic marker *placenta growth factor* Have been demonstrated to be useful tools for the prediction of preeclampsia and the need for delivery *within 2 weeks*.

before 34 weeks, *sFlt-1:PlGF ratio greater than 85* had a sensitivity of 72.9% and specificity of 94% when *predicting adverse maternal and fetal outcomes*, including delivery within 2 weeks.

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Clinical features	Normal pregnancy	CKD	Lupus flare	Pre-eclampsia
Hypertension	No	Yes	Yes	Yes
Proteinuria	<300 mg per day	Yes	Yes	Yes
Haematuria	No	Yes	Yes	No
Increased serum creatinine	Physiological	Not above pre-pregnancy creatinine level	Yes	Yes
Rate of change in serum creatinine	Third trimester	None unless disease progression or superimposed acute injury	Can be rapid (hours or days)	Can be rapid (hours or days)
Skin	Hyperpigmentation, striae	No	Malar rash, discoid lupus, acute cutaneous lupus	No
Joints	Mechanical pain	No	Arthritis	No
Hair loss	Yes (post-partum telogen effluvium)	No	Yes	No
Haemoglobin	Iron-deficiency anaemia	Erythropoietin deficiency	Anaemia of chronic disease, haemolysis	Haemolysis
Platelets	Gestational thrombocytopenia	Normal	Thrombocytopenia	Thrombocytopenia
Other blood tests	↑ESR	↓eGFR prior to pregnancy	• ↓Complement • ↑dsDNA	• Transaminitis • ↓PLGF • ↑sFLT1

Decreasing Preeclampsia Risk

prescribe acetylsalicylic acid to any pregnant Woman with CKD because of a higher pre eclampsia risk.

Start prophylactic ASA in doses of 80 to 150 mg/day from *12 weeks* (after last menstruation) and preferably *before the end of the sixteenth* week.

Stop the treatment at least 1week before the expected natural birth or planned cesarean section, that is, usually at 36 weeks pregnancy.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

Decreasing Preeclampsia Risk

recommend to use *at least 1000 mg/day of elemental calcium* (preferably in their food) because this may lower the preeclampsia risk.

patients should not take calcium supplements at thesame time as iron supplements, which should be taken on an empty stomach.

do not recommend sodium or protein restriction to prevent preeclampsia.

If necessary, recommend this as part of their CKD treatment

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

Anemia

Aim at a ferritin level >80 mcg/l to 500 mcg/l in pregnant patients with CKD with intact renal function*[eGFR] >60; G1-2*) and anemia.
Aim at a ferritin level >200 mcg/l to 500 mcg/l In pregnant patients with CKD with *(eGFR <60; G3-5ND)* and anemia.

do not prescribe iron in pregnant patients with CKD with ferritin level >500 mcg/l and/ or *transferrin saturation >30%*.

Aim at a transferrin saturation between 30% and 50% and a ferritin level >300 mcg/l to 800 mcg/l in pregnant *dialysis patients* with anemia.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD,Kidney International Reports (2022)

Anemia

Aim for an Hb of 6.2 to 6.8*mmol/l* (corresponding with an *Ht* of 30% to 35%) in pregnant patients with CKD (with or without dialysis),

Because of erythropoietin resistance during pregnancy,consider increasing the rhEPO dose For pregnant patients who already used rhEPO Before pregnancy by *50% to 100%.*

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)
Handbook of Dialysis Therapy 2023

Anemia

for pregnant patients with CKD, perioperative transfusions should be given if *Hb <4.5 mmol/l* and considered if *Hb <5.0* mmol/l in a stable situation. consider transfusions if Hb<6.0 mmol/l and major blood loss is expected (e.g.,around birth)

consider blood transfusions for pregnant dialysis patients if their Hb <6.0 mmol/l and it cannot be expected that Hb can be corrected within a few weeks .
always give blood transfusions if Hb <6.0 mmol/l and major blood loss is expected (e.g.,around birth).

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Pregnancy in women with kidney transplants

Transplantation restores fertility, and although most women with kidney transplants can deliver successfully,

there is a *higher risk* of miscarriage, therapeutic abortion, stillbirth, ectopic pregnancy , preterm birth, *low birth weight babies*, and neonatal death.

Recommendations regarding health status for pregnancy in kidney transplant recipients :

Good general health for *2 years post-transplantation*, with serum *creatinine levels below 2.0 mg/dL* (preferably < 1.5 mg/dL)

No recent acute rejection or ongoing rejection

Normotension, or hypertension controlled with minimal antihypertensive agents.

No or minimal proteinuria

No evidence of pelvi caliceal dilatation on renal ultrasonogram

Recommended immunosuppression includes the following:

Prednisone – *Less than 15 mg per day*

Azathioprine – *2 mg/kg/d or less*

Kidney desease and Pregnancy,Medscape 2023

Pregnancy in women with kidney transplants

Breast-feeding on *cyclosporine is not recommended* ; *tacrolimus* may be taken during breast-feeding, though monitoring of infant levels is recommended.
Mycophenolate mofetil and sirolimus should be discontinued for *6 weeks* prior to conception
The following are complication risks in kidney transplant recipients:

Preeclampsia occurs in approximately one *third* of kidney transplant recipients.
almost 50% of pregnancies in these women end in *preterm delivery due to hypertension*.

an increased risk of cytomegalovirus, toxoplasmosis,and herpes infections, which raise concern for the fetus.

Kidney desease and Pregnancy,Medscape 2023

Medication	Periconceptional advice	Known teratogenicity	Possible effect on neonate	Pregnancy advice
Corticosteroids	Can be used		With chronic use of prednisone dose >10 mg association with fetal growth restriction and neonatal adrenal suppression	Can be used
Azathioprine	Can be used	No	Association of maternal leukopenia with neonatal leukopenia and pancytopenia	Can be used; if leukopenia: decrease dose in 3rd trimester to prevent neonatal problems after birth
Tacrolimus	Can be used	No	Association of maternal hyperkalemia with neonatal hyperkalemia and mild renal dysfunction	Can be used; increase dose from 1st trimester on basis of trough level
Mycophenolae mofetil	Contraindicatin ; *stop at least 3months before conception* and switch to safer alternative	Associated with *congenital defects in face, extremities, heart,esophaus and kidneys*	–	Absolutely contraindicated

Medication	***Periconceptional advice***	Known teratogenicity	Possible effect on neonate	Pregnancy advice
Cyclofosfamide	Discouraged	Association with congenital defects	—	Discouraged, use only with strict indication in 2nd or 3rd trimester(life threatening situations)
IVIG	Can be used	No	_	Can be used
Ciclosporine	Can be used	No	Association with *neonatal leukopenia*	Can be used; *increase dose from 1st trimester* on basis of trough levels

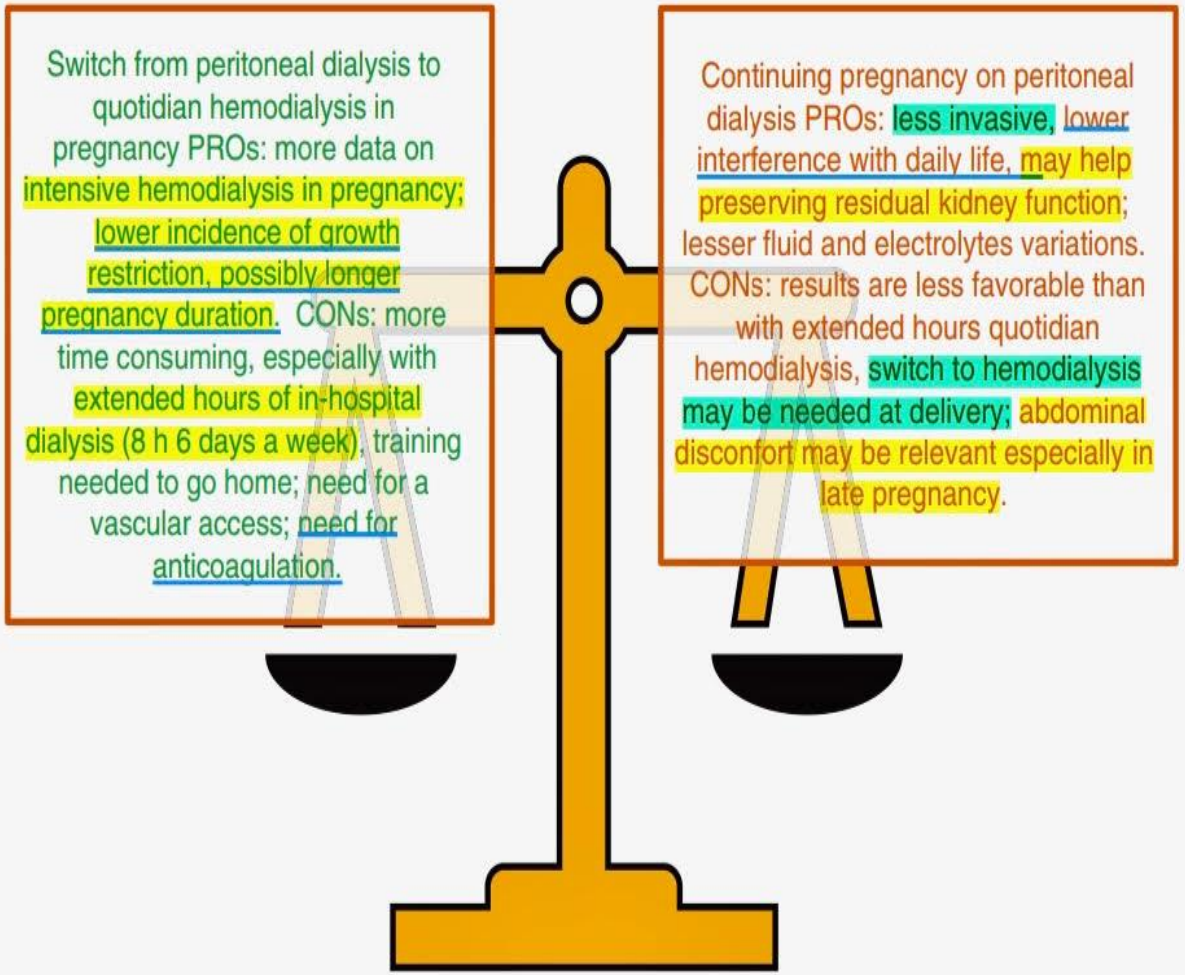
Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Dialysis

In hemodialysis patients who want to become pregnant, consider whether a kidney transplant is possible and whether pregnancy can be postponed *until 1 year after transplantation* because the pregnancy outcomes after kidney transplantation better than during hemodialysis

preferably treat pregnant dialysis patients with intensive hemodialysis instead of peritoneal dialysis

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)



• **Fig. 57.5** Pros and cons of switching from peritoneal dialysis to hemodialysis in pregnancy.

Dialysis

depending on *their residual renal function*, intensify the hemodialysis schedule of pregnant patients to *at least 20 hours/week* so that the maternal urea level will always be *lower than 17.5 mmol/l* from the second trimester onwards.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Dialysis

the Toronto experience provides clear data on the best dialysis schedule in pregnancy in patients

without residual clearance.

hemodialysis should be performed *8 hours* per session,

6 or 7 days per week.

the results of pregnancy improve along with the increase in frequency of dialysis sessions, and reaching statistical significance *at or above 36 hours per week.*

for example, frequent night dialysis.

Handbook of Dialysis Therapy2023

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Dialysis

The use of Kt/V or urea levels for tailoring dialysis is not recommended, and a *predialysis urea level below 100 mg/dL* (*BUN < 50* mg/dL) is commonly used as a surrogate marker of dialysis efficiency on the basis of the Canadian experience.

bicarbonate levels should be carefully monitored due to the risk of inducing alkalosis and, as a starting point, should be *reduced to 30–32* MEq/L. due to the risk of depletion of *potassium levels*,on extended-hours daily dialysis, a concentration of *3.5 mEq/L* should be the reference

Dialysis

consider starting intensive hemodialysis for pregnant women with severe kidney failure who are not on dialysis yet, if despite an adequate low protein diet the maternal urea level cannot be maintained below 17.5 mmol/l

Dialysis Membranes

the most often employed terms are

“high flux,” “*high permeability*,” and

“*biocompatible* membranes.

however, there are no studies reporting on membrane size with respect to body size and

the balance between depuration and loss of nutrients.

Dialysis Membranes

There are *no data* on the use of low-permeability membranes for reducing the loss of albumin and potentially important nutrient.

What we know:

Intensive dialysis is usually performed with *high flux membranes* and the best results are obtained in this context.

during intensive dialysis , the loss of nutrients may be important with a need for supplementation of phosphate and water-soluble vitamins.

Dialysis

double the dosages of water-soluble vitamins

for pregnant patients treated with intensive hemodialysis and start with deliberately high doses of *folic acid (5 mg/day*) even before conception because these substances will be removed in higher quantities by *high-intensity hemodialysis*.

patients treated with intensive hemodialysis should have a daily protein intake of *1.5 to 1.8* g/kg ideal weight per day.

Summary of the Dutch Practice Guideline on Pregnancy Wish and Pregnancy in CKD Kidney International Reports (2022)

Conclusions

Future research is required into the mechanisms and management of impaired fertility in CKD, preferential choices and optimal dosage of therapeutic agents for the management of hypertension, and the pathophysiology and prevention of progressive renal deterioration in pregnancy.


THANK
YOU!