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Беременность при ХБП 4 стадии: серия наблюдений специализированного нефрологического центра

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Pregnancy in chronic kidney disease stage 4: a case series from a referral center

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Ключевые слова: *хроническая болезнь почек, артериальная гипертензия, преэклампсия, беременность*

Резюме

Цель: **беременность у женщин с поздними стадиями хронической болезни почек (ХБП) связана с высоким риском неблагоприятных исходов для матери и плода. Потенциальным фактором, определяющим результат ведения беременности, является организация медицинского наблюдения, однако данные о тактике ведения беременности у женщин с додиализными стадиями ХБП все еще ограничены. В данном ретроспективном исследовании мы поставили цель проанализировать течение и исходы беременности у женщин с ХБП 4 стадии.**

Материалы и методы: **13 беременных женщин с ХБП 4 стадии наблюдались в центре помощи беременным женщинам ГКБ им. А.К. Ерамишанцева. Оценивали: причину ХБП, акушерский анамнез, креатинин сыворотки до беременности (sCr), срок беременности при первом посещении, протеинурию, sCr и артериальное давление (АД) в каждом триместре, срок родоразрешения и исход беременности. Физиологическим ответом почек на беременность считали стойкое снижение SCr на ≥10 мкмоль/л от догестационного уровня. Развитие преэклампсии диагностировали на основании резкого повышения артериального давления, протеинурии и/или sCr вместе с изменением ангиогенного коэффициента (в некоторых случаях). Ведение беременности включало контроль АД, коррекцию анемии, антиагрегантную и антикоагулянтную терапию, лечение инфекций мочевыводящих путей.**

Результаты: **артериальная гипертензия на момент обращения имела место в 6 из 13 случаев, среднее АД снизилось к 3 триместру на фоне лечения. Протеинурия увеличивалась во время беременности во всех случаях, более быстро у женщин, у которых впоследствии развилась преэклампсия. Уровень sCr в среднем на момент направления в центр составил 184±13,3 мкмоль/л, мочевина 9,8±0,6 ммоль/л, рСКФ 32,9±2,9 мл/мин/1,73 м^2. После родов sCr увеличился до 243,4±37,8 мкмоль/л, мочевина 11,9±0,7 ммоль/л, рСКФ снизилась до 21,8±1,4 мл/мин/1,73 м^2. Средний срок родов составил 34 недели гестации. Преэклампсия диагностирована в 6 случаях. Все новорожденные были живы и жизнеспособны. Ни одна из пациенток не нуждалась в диализе во время беременности или сразу после родов.**

Заключение: **благоприятный исход беременности, определяемый как рождение жизнеспособного ребенка, возможен у женщин с 4 стадией ХБП, однако в большинстве случаев родоразрешение происходит преждевременно, а у матери отмечается прогрессирующее снижение функции почек.**

Abstract

Objective: **pregnancy in women with advanced chronic kidney disease (CKD) is associated with a high risk of adverse outcomes for the mother and the fetus. Setting of care is a potential determinant of the results, but data about pregnancy course in different settings are still limited. In this retrospective study, we aimed to analyze the course and outcomes of pregnancy in women with CKD stage 4 followed-up in a referral center in Russia.**

Materials and methods: **thirteen pregnant women with CKD stage 4 were followed in a dedicated unit for pregnant women with kidney diseases. Main data collected: CKD cause, obstetric history, pre-gestational serum creatinine (sCr), week of gestation at the first visit, proteinuria, sCr and blood pressure (BP) at referral and each trimester, type and week of delivery and pregnancy outcome. Physiological kidney response to pregnancy was considered as a persistent decrease of SCr by ≥10 μmol/L from the pre-gestational level. Superimposed PE was diagnosed based on the abrupt increase of blood pressure, proteinuria and/or sCr, together with alteration of the angiogenic-antiangiogenic ratio, whenever available. Pregnancy management included BP control, anemia correction, antiplatelet and anticoagulant therapy, and urinary tract infection treatment.**

Results: **arterial hypertension was present at referral in 6/13 cases, the mean BP decreased by the 3-rd trimester under treatment. Proteinuria increased during pregnancy in all cases, more rapidly in women who subsequently developed preeclampsia. Mean sCr at referral to the center was 184±13.3 μmol/L, urea 9.8±0.6 mmol/l, eGFR 32.9±2.9 ml/min/1.73 m^2. Postpartum sCr increased to 243.4±37.8 μmol/L, urea 11.9±0.7 mmol/L, and eGFR dropped to 21.8±1.4 ml/min/1.73 m^2. Median term of delivery was 34 weeks of gestation. Superimposed preeclampsia was diagnosed in 6 cases. All newborns were alive and viable. None of the patients needed dialysis during pregnancy or immediately after delivery.**

Conclusion: **a favorable pregnancy outcome, defined as a viable baby without major health issues, is possible in women with CKD stage 4, however prematurity is common, and a decrease in the kidney function is observed in most of the cases.**

Key words: *chronic kidney disease, hypertension, preeclampsia, pregnancy outcome*

Introduction

It is generally accepted that fertility decreases in women with chronic kidney disease (CKD) along with the progression of CKD, and the prevalence of advanced CKD in pregnant women is considered relatively low. Nevertheless, the number of reports of pregnancies not only in women with the early stages of CKD, but also in women with advanced CKD stages, and even on kidney replacement therapy by dialysis is increasing [1-5].

Since the policy towards dialysis initiation differs in patients with CKD stage 5, focusing on CKD stage 4 may allow increasing our understanding of the complex relationships between kidney and placenta, and of the effect of different follow-up policies in patients with advanced CKD. However, the number of observations of pregnancies in women with advanced CKD remains scarce. For instance, Mexican authors describe 7 cases [6], Russian researchers report 4 cases [7], the largest Italian cohort included 10 women with CKD in stages 4 and 5 [8], and the largest recent series from the UK reported on 25 patients with CKD stages 4 and 5 [9].

While general indications for the management of pregnancy in CKD patients have been published, each CKD stage has its own peculiarities, and further research is needed in this area, to allow improving pregnancy outcomes. Thus, we aimed to analyze pregnancy course and outcomes in women with CKD stage 4, followed in a recently established Center dedicated to providing outpatient multidisciplinary consultations for pregnant women with CKD, in a public hospital in Moscow, Russia.

Materials and methods

Setting of care

The Unit for care for pregnant women with CKD was established in 2018 at the Moscow City Clinical Hospital named after A.K. Eramishantsev, which is one of the largest hospitals in Moscow city. The nephrology unit has 40 beds, the hemodialysis service provides 70-75 hemodialysis sessions per day, and the maternity unit is specialized in assisting women with high risk pregnancies, and in particular with kidney diseases. The mean number of deliveries is 6000 per year. The hospital has dedicated wards for internal medicine, endocrinology, cardiology, neurology, surgery and urology, and intensive care units (ICU), including ICU for the newborns, and offers consultations of rheumatologist and hematologist. The team of the Unit for pregnant women with CKD encompasses four nephrologists, providing mainly outpatient consultations; nephrologists and obstetricians manage pregnant women admitted to the nephrology or obstetrics unit jointly. In cases with concomitant urological problems or other issues, other specialists are involved in the management of the patients.

Patient selection

The electronic database of the nephrology center for pregnant women encompasses 5992 records of 5157 women with a suspected kidney disease due to different abnormalities in the blood and/or urine tests, referred by the obstetricians in 2018-2022. The most common cause of referral was bacteriuria, and less frequently gestational proteinuria. CKD was diagnosed in 224 women; stage 1-2 in 189 cases, stage 3 in 22 cases, and stage 4 in 13 cases. There were no women with CKD stage 5 at the time of preparing this manuscript.

For the purpose of this retrospective study, we focused on the women with CKD stage 4, and analyzed the course and outcomes of their pregnancies.

The CKD stage was defined whenever possible on data available before pregnancy according to the eGFR (CKD-EPI: n=7; 53.8%), or, if available, according to the endogenous creatinine clearance (n=3; 23.1%). In three cases (23.1%) the baseline kidney function data were not available, and we considered the eGFR values found at the referral visit to the nephrologist in the first trimester of pregnancy.

Main data collected

The following data collected from the patient's electronic charts: CKD cause; previous obstetric history; pre-gestational serum creatinine (sCr) level; term of gestation at the first visit to nephrologist; proteinuria, hemoglobin (Hb), sCr and blood pressure (BP) at the first visit and during pregnancy; delivery term; and pregnancy outcome. BP was monitored at each visit. Kidney function was assessed by sCr level and estimated glomerular filtration rate (eGFR). Unfortunately, our center does not carry out the clearance method for calculating GFR, so we used the CKD-EPI equation. We also checked the angiogenic-antiangiogenic ratio (sflt1-PlGF) whenever possible, in particular in cases with a clinical suspicion of preeclampsia.

Pregnancy course definitions

A physiological kidney function response to pregnancy was defined as a persistent decrease of sCr in the first and second trimesters of at least 10 μmol/L from

the pre-gestational level, or from the first value, if obtained in the first trimester.

There is no universally accepted definition of pre-eclampsia (PE), superimposed on CKD [9]. Since almost all of our patients demonstrated an increase of proteinuria during the course of pregnancy, we did not take into account proteinuria alone as a diagnostic criterion for PE. Since antihypertensive drugs tightly controlled BP in our patients, the criterion of BP increase was also difficult to apply. Therefore, while considering increase of proteinuria and BP as ancillary criteria, we diagnosed superimposed PE based on the abrupt increase of sCr taken together with changes of the angiogenic-antiangiogenic ratio (sflt-1/PlGF) [Automated modular platform Roche Cobas 8000 with e801 immunochemical module, Roche Diagnostics, Switzerland], whenever available; at least one assessment in pregnancy was available in 9 out of 13 patients.

Management of pregnant women with CKD

In each case, both pre-conception and, when the former was not possible, at referral, counseling was performed, and the main potential complications of pregnancy were discussed with the patient and her family. According to the Russian Ministry of Health, if sCr level is >200 μmol/l, the physicians must offer the option of termination of pregnancy at any term of gestation due to the high risk of maternal complications. If the patient is willing to continue pregnancy, an individual management plan, which includes comprehensive clinical and laboratory controls every 2 weeks, is agreed at counseling.

Acetylsalicylic acid is prescribed by the nephrologists at a dose of 75-150 mg per day at the first visit. Low molecular weight heparin in prophylactic doses is also routinely prescribed since pregnancy diagnosis in the absence of contraindication, aiming to ameliorate placental perfusion.

Treatment of arterial hypertension follows the European Society of Cardiology Cardiovascular Diseases during Pregnancy (Management of) Guidelines [10]; methyldopa is the first choice (maximum 2000 mg per day). Target BP values are considered 115-135/75-85 mm Hg.

Anemia (defined as Hb <11.0 g/dL) treatment includes oral iron supplementation, intravenous iron is used if Hb drops to <90 g/L and ferritin level is low; all women are advised to take 400-800 μg of folic acid per day throughout pregnancy. Vitamin B12 (normal rang 87-883 pg/ml) is checked at baseline, monitored if needed, and supplemented if necessary; and erythropoietin-stimulating agents are added in case of persistent anemia without iron and/or vitamin deficiency.

In cases of secondary hyperparathyroidism alfacalcidol is prescribed, and in the absence of hypercalcemia (total serum calcium >2.5 mmol/l), calcium carbonate and cholecalciferol are added.

The first choice of antimicrobial therapy in case of positive urinary cultures is cephalosporins of 3-4 generation.

Nutritional management: we recommended a moderate restriction of protein intake, corresponding to a "normal intake" for CKD beyond pregnancy, which is 0.8-0.9 g of protein/kg/day preferably of vegetable origin. For women who were on a very low-protein diet (usually 0.6 g/Kg/day with ketoanalogues supplementation – commonly Ketosteril 100 mg/kg/body mass/day) before pregnancy, we recommended to keep this diet during pregnancy, while we do not recommend to increase the protein intake or ketoanalogues doses (11). In the presence of hyperuricemia (serum uric acid >350 μmol/L), a low-purine diet is prescribed, and an alkalizing drink – mineral water and/or soda (5 g per day) with lemon (1/2 fruit per day) is added.

Main laboratory parameters (Hb, sCr, uric acid, calcium, phosphate etc.) are usually monitored monthly, but frequency may be increased on demand.

Statistical analysis

Statistical analysis was performed using the SPSS Statistics Version 26 software, IBM, USA. The distribution was assessed using the Kolmogorov – Smirnov test and the Shapiro – Wilk test. Depending on the correspondence of the data to the normal distribution, the following calculated indicators were used: median [min; max], with data distribution that differs from normal, or Mean (±SD – standard deviation) with normal data distribution. The association between data was assessed by calculating Spearman's rank correlation ratio. Statistical significance was set at p=0.05.

Ethical issues

The Eramishantsev City Clinical Hospital Local Ethics Committee for Clinical Studies approved the present retrospective study (protocol № 9(1)-2021). Because this was a retrospective study, based on data from medical records, and no personal information was disclosed, patient's consent was not required, according to our institutional policy, considering that written informed consent for the use of anonymous information for research purposes is obtained from every patient at hospital admission.

Results

Baseline data

The prevalence of CKD stage 4 among our CKD patients was 5.8% (13 out of 224 women with CKD). The mean age of the 13 women included to the study was 33.4±5.2 years.

Body mass index was within the normal range (18.5-25 kg/m^2) in all patients. The most common causes of CKD were tubulointerstitial nephritis (4 cases) and chronic glomerulonephritis (3 cases), followed by diabetic nephropathy (2 cases), atypical HUS, polycys-

Table 1 | **Таблица 1**

Main laboratory data in thirteen CKD patients with stage 4 CKD at referral, during pregnancy, and after delivery

Основные лабораторные данные у 13-и пациенток с ХБП 4 стадии на момент обращения в Центр, во время беременности и после родов

Pt N	Age yr	CKD cause	sCr pre-gestational µmol/L	eGFR pre-gestational mL/min	ECrCl pre-gestational mL/min	sCr 1st trimester µmol/L	eGFR 1st trimester mL/min	sCr pre-delivery µmol/L	eGFR pre-delivery mL/min	sCr 3-6 months after delivery µmol/L	eGFR 3-6 months after delivery mL/min	Urea 1st trimester mmoL/l	Urea pre-delivery mmoL/l	PU 1st trimester g/L	PU 2st trimester g/L	PU pre-delivery g/L
1	30	GN	NA	NA	NA	192	29,7	260	20,6	306	16,9	11,0	13,2	NA	3,0	4
2	37	TIN	185	29,6	NA	154	37,1	214	24,8	520 (PD)	8,5	8,3	9,5	1,0	2,9	3,8
3	36	GN	178	31,2	29,1	149	38,7	207	26,0	220	24,1	9,0	11,8	3	2,0	2,9
4	29	TIN	252	21,5	NA	259	20,8	377	13,2	300	17,4	12,0	16,7	0,37	0,1	<0,1
5	35	TIN	210	25,7	NA	210	25,7	257	20,1	600 (HD)	7,2	11,0	12,3	1,35	3,2	0,8
6	38	ADPKD	180	30,3	28,1	154	36,6	190	28,4	214	24,6	7,0	12,0	1,5	2,0	2
7	30	DN	199	28,8	NA	113	57,1	145	42,3	196	28,9	10,0	11,5	2	2,1	2
8	42	aHUS	206	25,1	NA	NA	NA	168	32,1	205	25,2	NA	8,5	NA	NA	1
9	26	TIN	179	33,2	27,8	169	35,6	176	33,9	195	30,0	8,0	9,6	0	0,1	<0,1
10	27	CAKUT	NA	NA	NA	270	20,1	270	20,1	230	24,4	14,0	14,2	0,5	0,5	0,5
11	38	DN	210	25,2	27,6	188	28,8	220	23,8	205	25,9	12,0	11,8	1	2,3	2
12	28	APS	NA	NA	NA	202	28,3	220	25,5	201	28,5	8,0	13,2	1	2,0	2
13	38	GN	200	26,7	26,9	152	37,2	207	25,6	230	22,6	8,0	10,6	1,2	1,0	1,9

Legend: ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic-uremic syndrome; APS, antiphospholipid syndrome; CAKUT, congenital anomalies of kidneys and of the urinary tract; DN, diabetic nephropathy; ECrCl, endogenous creatinine clearance; eGFR, estimated Glomerular Filtration Rate; GN, glomerulonephritis; HD, hemodialysis; NA, not available-no data; PD, peritoneal dialysis; PU, proteinuria; sCr, serum creatinine; TIN, tubulointerstitial nephritis.
Условные обозначения: ADPKD, аутосомно-доминантная поликистозная болезнь почек; aHUS, атипичный гемолитико-уремический синдром; APS, антифосфолипидный синдром; CAKUT, врожденные аномалии почек и мочевыводящих путей; DN, диабетическая нефропатия; ECrCl, клиренс эндогенного креатинина; eGFR, расчетная скорость клубочковой фильтрации; GN, гломерулонефрит; HD, гемодиализ; NA, недоступно/нет данных; PD, перитонеальный диализ; PU, протеинурия; sCr, сывороточный креатинин; TIN, тубуло-интерстициальный нефрит.

Table 2 | **Таблица 2**

Blood pressure data in thirteen patients with stage 4 CKD at referral, during pregnancy, and after delivery

АД у 13-и пациенток с ХБП 4 стадии при первом обращении в Центр, во время беременности и после родов

Pt N	SBP 1st trimester mm Hg	SBP 2nd trimester mm Hg	SBP 3d trimester mm Hg	DBP 1st trimester mm Hg	DBP 2nd trimester mm Hg	DBP 3d trimester mm Hg
1	130	160	-	80	100	-
2	160	120	120	90	70	70
3	150	150	130	110	100	80
4	140	110	120	80	70	80
5	120	110	120	80	70	80
6	165	130	120	90	80	80
7	150	130	130	90	80	80
8	NA	NA	145	NA	NA	85
9	110	110	110	70	70	70
10	120	110	110	80	70	70
11	140	150	-	90	90	-
12	135	145	130	80	90	80
13	140	120	-	80	70	-

Legend: SBP, systolic blood pressure, DBP, diastolic blood pressure.
Условные обозначения: SBP – систолическое АД, DBP – диастолическое АД.

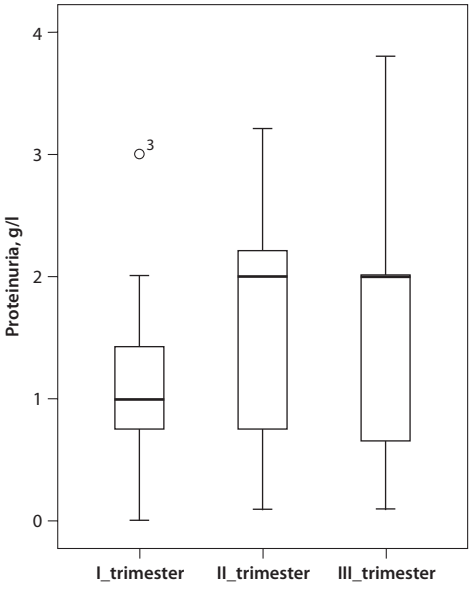

Fig. 1. Mean proteinuria values by trimester (g/l)

Рис. 1. Средние значения протеинурии по триместрам (г/л)

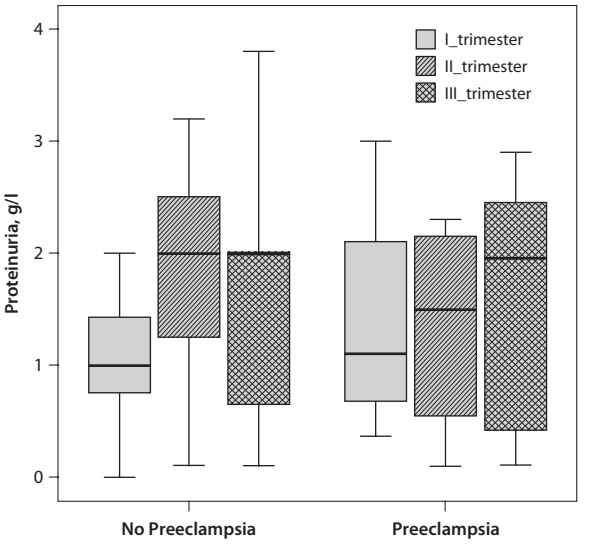

Fig. 2. Mean proteinuria values in women with and without preeclampsia (g/l)

Рис. 2. Средние значения протеинурии у женщин с преэклампсией и без нее (г/л)

tic kidney disease, congenital anomalies of kidneys and urinary tract and antiphospholipid syndrome-associated nephropathy (one case each). The mean gestation week at the first visit in nephrology was 15 weeks. Eight (61.5%) women were multigravida, and seven of them had a previous history of obstetric complications (arterial hypertension, preeclampsia, preterm birth, acute kidney injury). Mean laboratory data and blood pressure levels at the first visit are shown in the Tables 1 and 2.

Table 3 | **Таблица 3**

Blood pressure variation by trimester

Изменение артериального давления по триместрам

Blood pressure, mmHg	Number of patients 13 Mean value (Standard deviation)
I trimester	140/86 (±16/12)
II trimester	128/82 (±7/5)
III trimester	127/80 (±13/12)

Hypertension, proteinuria and kidney function in pregnancy

Arterial hypertension was present at the first visit in 6 out of 13 women (46.2%) (Table 2). The mean BP decreased by the 3-rd trimester (Table 3), also as an effect of the treatment, that was needed in 6 further cases, at a median gestational age of 17 weeks (alpha-methydopa in 4, bisorpolol and metoprolol in one each); beta-blockers were added on the top of methyldopa in 2 cases, because of adverse effects of calcium-channel blockers (tachycardia). One patient only remained normotensive throughout pregnancy (Table 2).

The mean proteinuria level increased in all cases, however proteinuria increased more sharply in six women who subsequently developed preeclampsia (PE) (Table 1, Figures 1 and 2).

The mean kidney function parameters prepregnancy, at the first visit, and during pregnancy are shown in Table 1 and Figure 3. Im-

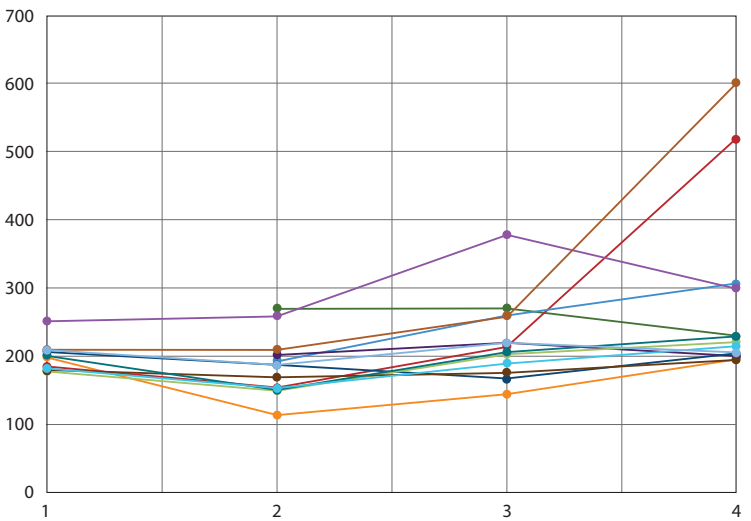

Fig. 3. Serum creatinine levels (μmol/L) pre-gestational (1), at the first trimester (2), before delivery (3), and 3-6 months after delivery (4)

Рис. 3. Уровни креатинина в сыворотке (мкмоль/л) до беременности (1), в первом триместре (2), до родов (3) и через 3-6 месяцев после родов (4)

Table 4 | **Таблица 4**

Clinical and delivery data in thirteen CKD patients with stage 4 CKD at referral, during pregnancy, and after delivery

Клинические и данные о родах у 13-и пациенток с ХБП 4 стадии

Pt N	Age yr	CKD cause	PE (and week of onset)	sflt1/PlGF (week)	Indication for delivery	Week of delivery	Type of delivery	Baby weight g	Centile %
1	30	GN	<34 wk	NA	PE	30	CS	1280	50
2	37	TIN	No	3,8	CKD progression	35	CS	2540	50
3	36	GN	<34 wk	3,9 (26 wk)	PE	33	CS	1540	10
4	29	TIN	<34 wk	186,2 (33 wk)	PE	33	CS	1840	30
5	35	TIN	No	NA	CKD progression	34	CS	1770	10
6	38	ADPKD	No	2,1	In term	38	VD	2700	15
7	30	DN	No	NA	PI	33	CS	2245	50
8	42	aHUS	>34 wk	NA	PE at 37 wk	37	CS	2250	5
9	26	TIN	No	13,1	In term	37	CS	2850	50
10	27	CAKUT	No	1,87	In term	38	CS	3300	70
11	38	DN	<34 wk	5,34 (21 wk)	PE	29	CS	950	15
12	28	APS	No	4,01	PI	34	CS	1750	15
13	38	GN	<34 wk	21,5	PE	30	CS	1000	15

Legend: ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic-uremic syndrome; APS, antiphospholipid syndrome; CAKUT, congenital anomalies of kidneys and of the urinary tract; CS, caesarian section; DN, diabetic nephropathy; GN, glomerulonephritis; NA, not available-no data; PE, preeclampsia; PI, placental insufficiency; sflt1/PlGF, angiogenic-antiangiogenic ratio; TIN, tubulointerstitial nephritis; VD, vaginal delivery; Wk, week of gestation.

Условные обозначения: ADPKD, аутосомно-доминантная поликистозная болезнь почек; aHUS, атипичный гемолитико-уремический синдром; APS, антифосфолипидный синдром; CAKUT, врожденные аномалии почек и мочевыводящих путей; CS, кесарево сечение; DN, диабетическая нефропатия; GN, гломерулонефрит; NA, недоступно/нет данных; PE, преэклампсия; PI, плацентарная недостаточность; sflt1/PlGF, ангиогенно-антиангиогенное отношение; TIN, тубуло-интерстициальный нефрит; VD, естественные роды; Wk, неделя беременности.

mediately postpartum, the kidney function decreased with respect to referral: sCr 243.4±37.8 vs 184±13.3 μmol/L, p^t=0,000 urea 11.9±0.7 vs 9.8±0.6 mmol/L; eGFR 21.8±1.4 vs 32.9±2.9 ml/min/1.73 m^2. At a subsequent check-up 3-6 month after delivery sCr remained stable (220.0 [195; 600] μmol/L, p^t=0.090). During pregnancy, the serum urea level did not exceed 17 mmol/L in any case (Table 1), and none of the patients needed dialysis before delivery. In two women (both with tubulointerstitial nephritis, and who did not develop PE) CKD progressed to stage 5 within the next 6 months after delivery and kidney replacement therapy was initiated (Table 1).

In 10 out of 13 women, the baseline pre-gestational sCr was available, which allowed assessing the kidney response to pregnancy. Six out of these 10 women demonstrated a decrease of sCr level in the 1-st and 2-nd trimester (Table 1), with the mean decrease of -19.5 μmol/L.

Pregnancy outcomes

The main outcome data and sflt1/PlGF ratio (when available) and shown in Table 4. The mean delivery term was 34 weeks of gestation. Only four women delivered at term: in one case delivery was vaginal, in two cases Cesarean section was needed for obstetric indications (previous Cesarean section or insufficient cervical dilatation), and in one case Cesarean section at week 37 was needed for preeclampsia. In the other 9 cases, indications for preterm delivery, in all by Cesarean section, were as follows: PE in 5 cases, placental insufficiency in 2 cases, and rapid progression of kidney disease in 2 cases. Evaluation of kidney function changes late after delivery was beyond the scope of this study, however we followed 9 out of 13 women for 3 years, and in 4 cases ESKD developed, and 5 patients are on follow-up for CKD stages 4 and 5.

All newborns were alive and viable with the median weight of 1840 grams [min: 950; max: 3300], the mean centile was 29.6 (±5.9), and only three babies had a birth centile of 10 or less; ten newborns needed intensive care, mainly because of prematurity. No child was born with malformations, and all were alive at the post-partum visit within 3-6 months from delivery.

Discussion

CKD is a growing problem encountered in pregnancy, possibly also because of the increased awareness of its importance [11, 12]. While the risk of adverse pregnancy-related outcomes increases with the progression of CKD, data regarding advanced CKD stages are still limited. The main factors usually considered as predictive of an increased risk of adverse pregnancy outcomes in women with CKD are proteinuria, reduced kidney function, and hypertension, especially if poorly controlled [8, 11].

With the aim of adding more information about the particular group of patients with advanced CKD, we reviewed the clinical data of 5992 women and focused on 13 pregnancies in CKD stage 4, defining the stage, when possible, before pregnancy. The importance of

pre-pregnancy staging should be underlined, as at the time of the first examination during pregnancy, the mean eGFR in patients previously staged as CKD 4 corresponded to CKD 3b, in keeping with the presence of a physiological response in most of the patients with advanced CKD [9, 14, 15].

The main pregnancy outcomes were relatively favorable: the mean term of delivery was 34 gestational weeks (GW) (one baby only was born at <30 GW, at 29 GW); 4 babies were born at term (37-38 weeks).

Likewise, the birth centile (mean 29.6±5.9) was reassuring, with only three babies with a birth centile less than or equal to 10. However, the newborns' body weight (median 1840 g, min 950 g; max 3300 g) was relatively low and 10 newborns needed intensive care, mainly because of prematurity. However, all children were alive at the post-partum visit within 3-6 months from delivery. In keeping with data form a larger series from Italy, the moderate reduction in protein intake does not seem to have affected the foetal growth, as one baby only was at the 5th centile, and 2 further ones were at the 10th.

Thus, data reported in our case series are in keeping with those reported in previous publications with advanced CKD [5, 8, 9, 16]. Further in keeping with literature data, no congenital malformation was found in the offspring [17, 18]. Of note, our patients were relatively old (33.4 years), and 8/13 were multiparous; in keeping with the presence of acknowledged and unacknowledged risks lined to CKD in pregnancy, 7/8 of these women had a complicated previous pregnancy (all of them followed up in other settings).

We further analyzed proteinuria, BP and SCr changes.

In the 1-st trimester the mean levels of proteinuria exceeded 1 g/L and increased thereafter (Figure 1). The level of proteinuria did not depend on the CKD cause. This finding could be explained, at least partially, by the development of PE in 6/13 of our patients. However, proteinuria increased even without PE, in patients with glomerulopathies and with other kidney diseases, which could suggest a role of glomerular endotheliosis. Almost two decades ago, Strevens et al found histological features of endotheliosis not only in cases of PE, but also in women with gestational hypertension, and in 7 out of 12 healthy pregnant women; the authors supposed that endotheliosis, beyond hypertensive pregnancy disorders, may accompany pregnancy as such [19]. However, in the absence of a kidney biopsy no conclusion can be drawn.

As for blood pressure changes it is worthy to note that while at the first visit, 6/13 women had high blood pressure, and that carefully selected and titrated antihypertensive treatment stabilized blood pressure to the end of the 2-nd trimester in all cases.

As for kidney function, 6 out of our 10 patients with available pre-pregnancy data demonstrated a physiological response to pregnancy. The small size of our series did not allow us confirming the correlation between the physiological response and development of preeclampsia, which we previously described in pregnant women with CKD stage 3a-4 [20]. Unfortunately, Sflt1/PlGF was tested only once and at different terms of gestation, thus not allowing concluding on its predictive value in our case series. Of note, the diagnosis of superimposed preeclampsia in women with CKD is difficult and there is no agreed definition CKD, which may also contribute to the differences among reports [21].

In spite of the PE related increase in serum creatinine, none of the patients needed dialysis in pregnancy, and only two of them started it within an overall follow-up of about 6 months. While our Center applies a policy of "intent to defer" dialysis start in pregnancy, in none of the cases the urea level was in the range some authors consider as indicating the need for dialysis start.

In conclusion, despite the high risk of adverse pregnancy outcomes, delivery of a healthy baby is possible in women with CKD stage 4 under careful monitoring by a multidisciplinary medical team, without immediate introduction of dialysis therapy. An increase of proteinuria is not necessarily associated with the development of preeclampsia.

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