Clinical Kidney Journal

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LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2021, vol. 14, no. 4, 1255–1260

doi: 10.1093/ckj/sfaa113
Advance Access Publication Date: 20 August 2020
Original Article

ORIGINAL ARTICLE

Pregnancies in kidney transplant recipients with complement gene variant-mediated thrombotic microangiopathy

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ABSTRACT

Background. Pregnancies in patients with complement gene variant-mediated thrombotic microangiopathy (cTMA) are challenging, and pregnancies in such patients after kidney transplantation (KTX) are even more so.

Methods. We identified nine pregnancies following KTX of three genetically high-risk cTMA patients enrolled in the Vienna thrombotic microangiopathy cohort. Preventive plasma therapy was used in three pregnancies, and one patient had ongoing eculizumab (ECU) therapy during two pregnancies.

Results. Seven out of nine pregnancies (78%) resulted in the delivery of healthy children. The other two included one early abortion at gestational Week 12 during ongoing ECU therapy and one late foetal death at gestational Week 33 + 3, most likely not related to complement dysregulation. Kidney transplant function after delivery remained stable in all but one pregnancy. In the aforementioned case, a severe cTMA flare occurred after delivery despite use of preventive plasma infusions. Kidney graft function could be rescued in this patient by ECU. As such, successful pregnancies can be accomplished in kidney transplant recipients (KTRs) with a history of cTMA. We used preemptive plasma therapy or ongoing ECU treatment in selected cases.

Conclusions. Thus, becoming pregnant can be encouraged in KTRs with native kidney cTMA. Extensive preconception counselling, however, is mandatory in such cases.

Received: 31.1.2020; Editorial decision: 30.4.2020

Keywords: atypical haemolytic uraemic syndrome, complement system, delivery, eculizumab, gravidity, kidney transplant recipient, neonate, pregnancy, pregnancy-associated complement gene variant-mediated thrombotic microangiopathy, thrombotic microangiopathy

INTRODUCTION

A diagnosis of complement gene variant-mediated thrombotic microangiopathy (cTMA) or atypical haemolytic uraemic syndrome bears a high risk for end-stage renal disease (ESRD); recurrence and graft loss following kidney transplantation (KTX); maternal and foetal complications due to pregnancy-related flares of cTMA in kidney transplant recipients (KTRs); and for maternal and foetal complications related to pre-pregnancy impaired kidney transplant function and immunosuppressive therapy [1–3]. Therefore, transplant physicians are somewhat reluctant to support the wish to have a child in female KTRs with a native kidney cTMA. Thus, data on clinical outcomes of pregnancies in KTRs with cTMA are scarce.

The largest series of pregnancies in women suffering from cTMA [4–7] or from thrombotic thrombocytopenic purpura [8, 9] did not report pregnancies in KTRs with a native kidney cTMA. In contrast, our group recently discussed maternal and foetal outcomes of 27 pregnancies in 14 women with a diagnosis of cTMA, which also included pregnancies of KTRs [1]. We here specifically extend this earlier observation and report detailed delivery outcomes of successful pregnancies in genetically high-risk KTRs with a native kidney cTMA enrolled in the Vienna thrombotic microangiopathy (TMA) cohort (Supplementary data, Figure S1). We further embark on management strategies and discuss pros and cons of the desire to have a child in such women.

MATERIALS AND METHODS

From the Vienna TMA cohort, which was established in 2014 at the Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna [1, 2], and includes patients with all types of TMA, we identified women with a given diagnosis of cTMA who conceived after having received a kidney graft [10]. These patients were also enrolled in a separate pregnancy outcome study. Demographic, clinical and genetic data of the mothers and their offspring were retrieved from the electronic and paper-based healthcare records of our institution. The institutional review board (IRB) at the Medical University of Vienna approved the study (for the Vienna TMA cohort: unique IRB identifier: 1368/2014; for the pregnancy outcome study: unique IRB identifier: 1265/2014). Written informed consent was obtained from all patients.

Genetic analyses were performed at the Department of Laboratory Medicine at the Medical University of Vienna and the Research Laboratory of the Third Department of Internal Medicine, Semmelweis University in Budapest, as previously described [1].

Dependent on clinical judgement, patients either received plasma exchange (PE) or plasma infusions (PIs), eculizumab (ECU) and supportive therapy. In cases where the C5-antibody ECU was used, it was administered according to the manufacturer's instructions [11, 12].

Descriptive data are presented as count and frequency or as mean and standard deviation. We used MS Excel and IBM SPSS version 24.06 for data analysis.

RESULTS

We here report all nine prospectively followed pregnancies of three KTRs since 2010, who were enrolled in the Vienna TMA cohort and in a pregnancy outcome study. However, we excluded two other KTRs who conceived before 2010, although we have included some information on these cases in Supplementary data, Tables S1, S2, S3 and S4. Supplementary data, Tables S5 and S6 indicate the case numbers of our patients and pregnancies reported in other analyses of the Vienna TMA cohort [1, 2, 13].

Key demographic, genetic and kidney transplant-related data of three women with cTMA and pregnancies following KTX are indicated in Table 1. They were 21 ± 2 years of age at cTMA manifestation, 25 ± 1 years of age at KTX and 33 ± 4 years of age at their latest deliveries. Preventive plasma therapy was used in three pregnancies, and one patient had ongoing ECU therapy during two pregnancies. Seven out of nine pregnancies (78%) resulted in the delivery of healthy children at Week 38 ± 1 of gestation, all of them appropriate (AGA) or large for gestational age (LGA). Individual maternal and delivery outcomes are indicated in Tables 2 and 3. Table 4 depicts the immunosuppressive therapy before, during and after each pregnancy. The time course of serum creatinine and proteinuria is shown in Supplementary data, Figure S2.

The first patient, a 26-year-old African woman with a history of cTMA, received a deceased donor kidney graft without preemptive plasma therapy in 2006. Three years later she became pregnant and received prophylactic PIs from the time of presentation in gestational Week 14 and continued throughout pregnancy. Kidney graft and neonatal outcome were excellent. Later, she received no preemptive plasma therapy during four additional pregnancies. Pregnancies two, four and five were uncomplicated. The third pregnancy was terminated at gestational Week 33 due to foetal death, which was most likely related to an intrauterine infection. There were no clinical or laboratory signs of a cTMA flare at this time.

At the time of transplantation, our second patient, a Caucasian woman, was 25 years of age with a history of 6 years of dialysis. At the age of 19 years, just 1 year after delivery of her first child, dialysis began due to biopsy proven cTMA, most likely triggered by a urinary tract and vaginal infection [15]. Transplantation was facilitated by plasma therapy for prevention of cTMA recurrence, which was never completely weaned off. During the first weeks after transplantation, several biopsies showed Banff borderline and Banff 2A lesions that were treated with steroids . The initial therapy with calcineurin inhibitors was then changed to an mechanistic target of rapamycin (mTOR) inhibitor.

Three years later, she had the wish to become pregnant and a surveillance biopsy showed no signs of rejection or TMA at this time. Four years after transplantation, she became pregnant with her second child and plasma therapy was intensified at Week 12 of gestation. A healthy boy was delivered by Caesarean section at gestational Week 38. Serum creatinine, proteinuria and blood pressure slightly increased towards the day of delivery but returned to baseline thereafter. A biopsy, taken at 12 weeks after gestation because of proteinuria and the

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Table 1. Demographic and kidney transplant-specific data of three women with a history of native kidney cTMA and pregnancies following KTX

Characteristic	Case I	Case II	Case III
Age at diagnosis of cTMA, years	24	19	19
Native kidney biopsy	TMA	ND	TMA
Therapy of cTMA	No	PE	PE
Age at ESRD, years	24	20	19
Type of dialysis therapy	HD	HD and PD	HD
Age at KTX, years	26	26	23
Deceased donor	Yes	Yes	Yes
Donor age, years	58	50	50
Donor sex	Female	Female	Female
HLA-mismatch	1-2-0	1-1-1	1-2-1
PRA/DSA	No	No	No
Preemptive plasma therapy	No	PE/PI	PE/PI
Serum creatinine at 4 weeks after KTX, mg/dL	1.25	1.6	1.32
KTX vintage at last follow-up, years	13	10	6
Total number of pregnancies before KTX	0	1	0
Total number of pregnancies after KTX	5	2	2
Age at first pregnancy following KTX, years	30	29	28
Genetic variants			
CFH	c.1160-22_1160-19delTTAT, het[c]	p.N516K, het[b]	p.C1032[a], het[a]
CFH haplotype	–	H8, hom c.331C>T, het	H8, het
CFI	p.I416L, het[a] c.482 + 6C>T, het[c]	–	–
CD46	–	–	–
CD46 haplotype	ggaac, het	ggaac, hom	ggaac, hom
CFHR1,3	del, het	–	del, het

Genetic variant classification according to the American College of Medical Genetics and Genomics [14].
[a]Pathogenic.
[b]Likely pathogenic.
[c]Uncertain significance.
ND, not done; HD, haemodialysis; PD, peritoneal dialysis; PRA, panel reactive antibodies; het, heterozygous; hom, homozygous; del, deletion.

Table 2. Risk factors for pregnancy and maternal outcomes of nine pregnancies

Characteristic	Case-pregnancy number								
	I-1	I-2	I-3	I-4	I-5	II-1	II-2	III-1	III-2
Serum creatinine before pregnancy, mg/dL	1.12	1.29	0.88	1.02	1.11	1.85	1.81	1.1	1.1
Proteinuria before pregnancy, mg/g creatinine	0	33	71	77	80	172	216	79	127
CKD stage before pregnancy	G1A1	G1A1	G1A1	G1A1	G1A1	G3bA1	G3bA1	G1A1	G1A1
SBP before pregnancy, mmHg	120	127	114	115	120	140	130	137	134
DBP before pregnancy, mmHg	60	80	74	80	70	90	80	85	95
Pre-existing hypertension, yes/no	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diabetes before pregnancy, yes/no	No	No	No	No	No	No	No	No	No
BMI before pregnancy, kg/m^2	25	27	28	27	30	21	22	19	19
Smoking history before pregnancy, yes/no	No	No	No	No	No	No	No	No	No
Smoking during pregnancy, yes/no	No	No	No	No	No	No	No	No	No
Worsening of creatinine during pregnancy, yes/no	No	No	No	No	No	Yes	Yes	No	No
Worsening of proteinuria during pregnancy, yes/no	No	Yes	No	Yes	Yes	No	Yes	No	Yes
Worsening of CKD stage during pregnancy, yes/no	No	No	No	No	No	Yes	Yes	No	No
Worsening of blood pressure during pregnancy, yes/no	No	Yes	No	Yes	Yes	No	No	No	Yes
Serum creatinine after pregnancy, mg/dL	1.06	1.15	0.92	0.98	0.98	1.96	7.64	1.02	1.11
Proteinuria after pregnancy (persistent)	No	No	No	No	No	No	Yes	No	Yes
CKD stage after pregnancy	G1A1	G1A1	G1A1	G1A1	G1A1	G3bA2	G5A3	G1A1	G1A2
SBP after pregnancy, mmHg	130	130	116	115	138	140	130	125	130
DBP after pregnancy, mmHg	90	100	78	80	96	90	80	84	87

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Table 3. Delivery outcomes of nine pregnancies in three kidney transplant recipients with a history of native kidney cTMA

Characteristic	Case-pregnancy number								
	I-1	I-2	I-3	I-4	I-5	II-1	II-2	III-1	III-2
Year	2010	2011	2014	2016	2019	2013	2015	2018	2019
Outcome	Live birth	Live birth	IUFT	Live birth	Live birth	Live birth	Live birth	Miscarriage	Live birth
Gestational age at birth, weeks	37 + 3	40 + 3	33 + 3	36 + 0	38 + 2	38 + 3	38 + 0	<12 weeks	37 + 0
Mode of delivery	Vaginal	Vaginal	Vaginal	Vaginal (induced)	Vaginal	C-section	C-section	–	Vaginal
Apgar score at 1/5/10 min	9/10/10	9/10/10	0/0/0	7/8/9	9/10/10	9/10/10	9/10/10	–	8/10/10
Sex, female or male	Male	Male	Male	Male	Male	Male	Female	–	Male
Birth weight, g	3110	3956	2230	3410	4000	3030	3240	–	3082
Birth length, cm	51	52	46	49	51	51	49	–	50
Head circumference, cm	33	36	35	36	33	33	34	–	34
Assessment	AGA	AGA	AGA	LGA	LGA	AGA	AGA	–	AGA
Admission to NICU, yes/no	No	No	No	No	Yes	No	No	–	No

The mean birth weight was 3397 ± 370 g, mean birth length was 51 ± 1 cm and mean head circumference was 34 ± 1 cm.
NICU, neonatal intensive care unit; IUFT, intrauterine foetal death.

Table 4. Immunosuppressive and TMA-specific therapies at KTX as well as before, during and after pregnancy

Case-pregnancy number	Preventive therapies			
	Initial	Before pregnancy	During pregnancy	After pregnancy
I-1	DAC, SIR, MMF, STR	CSA, AZA, STR	PI, CSA, AZA, STR	CSA, AZA, STR
I-2	–	CSA, AZA, STR	CSA, AZA, STR	CSA, AZA, STR
I-3	–	CSA, AZA, STR	CSA, AZA, STR	CSA, AZA, STR
I-4	–	CSA, AZA, STR	CSA, AZA, STR	CSA, AZA, STR
I-5	–	CSA, AZA, STR	CSA, AZA, STR	CSA, AZA, STR
II-1	BAS, PE, TAC, MMF, STR	PI, CSA, AZA, STR	PI, CSA, AZA, STR	PI, CSA, AZA, STR
II-2	–	PI, CSA, AZA, STR	PI, CSA, AZA, STR	ECU, CSA, AZA, STR
III-1	BAS, PE, TAC, MMF, STR	ECU, CSA, AZA, STR	ECU, CSA, AZA, STR	ECU, CSA, AZA, STR
III-2	–	ECU, CSA, AZA, STR	ECU, CSA, AZA, STR	ECU, CSA, AZA, STR

DAC, daclizumab; BAS, basiliximab; SIR, sirolimus; TAC, tacrolimus; CSA, cyclosporin A; MMF, mycophenolate mofetil; AZA, azathioprine; STR, steroid.

presence of donor-specific antibodies (DSAs), showed no signs of humoral rejection or TMA. Plasma therapy was continued through her next pregnancy. In 2015, at the age of 32 years, her third pregnancy was uncomplicated until Week 30 of gestation. From this time point, creatinine, proteinuria and blood pressure increased, and she had several infections, but finally delivered a healthy girl by Caesarean section in gestational Week 38. She received 1600 mL of fresh frozen plasma before and on the day after delivery. She then developed a full-blown cTMA flare with an increase of serum creatinine >7 mg/dL due to a kidney transplant biopsy-proven TMA and received a first dose of ECU on Day 5 after delivery. Haematologic response was quickly achieved. Kidney transplant function improved significantly; however, it has not returned to pre-pregnancy levels despite ongoing treatment with ECU.

At the age of 24 years, the third patient, a Caucasian woman, received a deceased donor kidney after 4 years of dialysis therapy because of cTMA. Preventive plasma therapy was performed until 3 months after transplantation, when plasma intolerance prompted a change to preventive therapy with ECU. Kidney function was excellent, and 2 years later, in 2017, her first pregnancy was diagnosed around gestational Week 7, but she reported a spontaneous abortion before Week 12 of gestation. ECU was continued, and she became pregnant again, delivering a healthy child 1 year after her abortion. The dose of ECU was increased to 900 mg every week in Week 17 of gestation. Labour had to be induced at Week 37 + 0 of gestation because of a slight increase in blood pressure and proteinuria at the end of pregnancy. Details of complement-related analyses of the mother and the newborn were reported elsewhere [13]. A biopsy, taken 4 months after delivery because of persistent proteinuria and presence of DSA, did not show signs of humoral and cellular rejection or TMA; proteinuria improved thereafter.

DISCUSSION

Seven out of nine prospectively followed pregnancies (78%) after KTX resulted in the delivery of healthy children in three genetically high-risk cTMA patients. Preventive plasma therapy was used in three pregnancies, and one patient had ongoing ECU therapy during two pregnancies. Only one patient, who also received preventive plasma therapies, presented with a severe cTMA flare shortly after delivery, but ECU rescued kidney function.

As of September 2019, 51 patients with cTMA were enrolled in the Vienna TMA cohort, comprising a total of 212 prevalent

and incident patients with primary and secondary TMAs (Supplementary data, Figure S1). About 23 of the 32 female patients with cTMA are currently in reproductive age, among them 8 with a kidney transplant, and excellent graft function in 6 cases. In young women, advanced chronic kidney disease (CKD) or dialysis dependence is associated with impaired fertility, which is rapidly restored after successful KTX [16–18]. This scenario of improved quality of life and excellent graft function enables uncomplicated pregnancies in most instances, like in our three cases.

In our kidney transplant centre, pregnancies and outcomes of mothers and children are followed prospectively [1, 19]. Preconception counselling is mandatory for mothers soon-to-be, and focuses on the risks of CKD, hypertension and immunosuppression for pregnancy and delivery outcomes. For the subgroup of patients with native kidney cTMA, counselling is even more delicate because of the risk of disease recurrence during or after pregnancy with all the potential harmful effects on the child's and mother's health, as well as transplant kidney function. The genetic risk profile and individual history also need consideration in these patients. In stable patients without signs of complement activation such as microangiopathic haemolytic anaemia and without preemptive plasma or complement inhibition after transplantation, watchful waiting is an option. Other women may benefit from intensified plasma therapy [1] or from ongoing ECU therapy, such as Case III in this report. However, we recently discouraged pregnancy in a 30-year-old woman with cTMA (*CFH* p. S1191L, heterozygous; *CFH*-H3 risk haplotype, heterozygous) who received long-term prophylactic plasma therapy following KTX. She would have first needed assisted fertilization and second, presented with an increase of proteinuria and blood pressure after the switch of antihypertensive therapy and a change from mycophenolate mofetil to azathioprine in preparation for a long-awaited pregnancy.

Limitations to this study include the different and somewhat inconsistent management of our patients, which is related to the very rare clinical setting we are reporting on. Although of interest with regard to the development of DSAs, we have not analysed human leucocyte antigen mismatches between the babies and grafts with the mothers.

In conclusion, becoming pregnant can be encouraged in KTRs with native kidney cTMA, given that kidney transplant function is excellent. Interdisciplinary care is mandatory and preemptive or therapeutic PE or complement blockade has to be initiated on an individual basis.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

We are grateful to our patients, who fully supported the data collection of their pregnancies and of their babies for this manuscript, and to Dorottya Csuka, Eszter Trojnár and Nóra Veszeli for genetic analyses. We also thank Leah Charlotte Piggott for language editing of the manuscript.

FUNDING

Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, Projekt-Nr: 14067.

CONFLICT OF INTEREST STATEMENT

None declared.

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