

Journal of Nephrologist



Pregnant kidney transplant recipients with COVID-19; a report of two cases and literature review

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ARTICLE INFO

Article type:
Case Report

Article history:
Received: 28 September 2021
Accepted: 28 January 2022
Published online: 2 February 2022

Keywords:
Coronavirus, Pregnancy,
Kidney transplant

ABSTRACT

If managing COVID-19 alone was a major challenge, one can expect an even greater challenge in certain scenarios, such as patients with kidney disease - including kidney transplant recipients (KT) - or pregnant women. When things could not get any worse, we just met the peculiar art of overcomplicating things: pregnant kidney and simultaneous kidney-pancreas (SKP) transplant recipients with COVID-19. Gleeson and colleagues (Imperial College, London) described the first similar case in April 2020. We describe two cases of pregnant KT and SKP transplant recipients with COVID-19, at different stages, and their evolution until delivery. Maternal and fetal outcomes are significantly affected by both KT and COVID-19, requiring a multidisciplinary approach with a well-trained team of obstetricians and nephrologists, as we will describe.

Implication for health policy/practice/research/medical education:

In this case report, we describe two cases of kidney/pancreas transplant recipients who acquired COVID-19 during pregnancy.

Please cite this paper as: Domingos A, Braga A, Gonçalves D, Pedrosa S, Martins LS, Braga J. Pregnant kidney transplant recipients with COVID-19; a report of two cases and literature review. J Nephrologist. 2022;x(x):e17291. DOI: 10.34172/jnp.2022.17291.

Introduction

Two years after COVID-19 was first identified, a broad range of manifestations have been related, from asymptomatic infection to severe multiorgan failure. Careful consideration must be given regarding certain populations, such as pregnant women or patients with chronic kidney disease (1).

While there is no increased risk of COVID-19 infection in pregnant patients, a worse clinical course has been described and mortality in symptomatic pregnant women might be higher than in non-pregnant individuals. However, most of them recover without hospitalization (2,3). The determination of maternal outcomes seems to be highly influenced by concomitant comorbidities, therefore risk factors for severe disease and death in pregnancy might include obesity, hypertension, diabetes, or older mean age (≥ 35 years) (4). Potential adverse effects on fetuses include, for instance, preterm birth, intrauterine

growth restriction (IUGR), or higher cesarean delivery rates (4).

Similarly, maternal and fetal outcomes are also significantly affected by kidney transplantation. Examples include lower pregnancy rates, higher preeclampsia rates, cesarean deliveries, preterm births, low-birth weight and fetal growth restriction (5).

At the same time, doubts remain about the susceptibility of solid organ transplant (SOT) recipients to COVID-19. Immunosuppression regimens, the need for regular presential visits and the high prevalence of comorbidities such as hypertension, heart disease, or diabetes might be related to higher infection rates (6). Raja and colleagues described a higher rate of admission in SOT recipients with COVID-19 (7). Although clinical features vary widely in this context, lymphopenia appears to be more common and more pronounced than in nontransplant patients with COVID-19 while fever appears to occur less frequently,

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possibly a consequence of immunosuppressive regimens (8). Morbidity and mortality data remain controversial and the outcome of kidney transplantation appears to be strongly influenced by concomitant comorbidities, as mentioned above. Recent studies by Rinaldi and colleagues suggest similar mortality between COVID-19-SOT recipients and the general population (8); identical results were described by Raja and colleagues (7). Avery and colleagues' studies showed that SOT recipients did not have worse outcomes than non-SOT patients hospitalized with COVID-19; further conclusions suggested that disease severity declined more rapidly over time in SOT recipients than in non-SOT patients (9).

Regarding immunosuppressive drug adjustments, the most consensual guidelines advise suspension of antiproliferative agents and possibly reduction or even suspension of calcineurin inhibitors (depending on disease severity) (10). The ideal management of glucocorticoid therapy is still unknown, since most centers choose to continue this practice because it is supported by current evidence which showing that its benefits outweigh risks (10). From another perspective, pregnant kidney transplantation recipients require timely modifications in immunosuppression, preferably before conception, such as switching from mycophenolate mofetil (MMF) to azathioprine (AZA) (5).

Considering a possible scenario of pregnant kidney and simultaneous pancreas and kidney transplantation transplant recipients with COVID-19, worse maternal and fetal outcomes could be expected.

Case Presentation

We describe two cases of pregnant kidney transplantation (KT) and simultaneous pancreas and kidney (SPK) transplant recipients with COVID-19, with different manifestations and outcomes. Clinical and biochemical data were collected from patient medical records.

Case 1

A 36-year-old nulliparous Caucasian woman, also an SKP transplant recipient due to type 1 diabetes diagnosed in infancy, became pregnant three years after transplantation. Several post-transplant urinary tract infections occurred in relation to detrusor hypoactivity; however, graft function was stable (serum creatinine of 0.8 mg/dL and urea of 33 mg/dL).

In March 2020, she reported to our transplant unit with a 3-day history of fever and myalgia, testing positive for COVID-19. Her immunosuppression regimen included tacrolimus (9 mg/d), prednisolone (5 mg/day) and AZA (75 mg/d, recently switched from MMF due to her wish to become pregnant). AZA was immediately discontinued until the infection cleared. She evolved well with no

hospitalization required. Shortly afterward, pregnancy was confirmed, about four weeks after the onset of COVID-19 symptoms. The pregnancy progressed without complications until the 35th week of gestation, when she was admitted to the maternal-fetal unit of our center for fetal monitoring due to fetal growth restriction. The pregnancy was terminated by cesarean section at 36 weeks of gestation due to abnormal cardiotocography, delivering a healthy male newborn weighing 2280 grams.

Case 2

A 34-year-old Caucasian woman, kidney transplantation recipient following end-stage renal disease due to reflux nephropathy, became pregnant 11 years after transplantation. She developed new-onset diabetes mellitus after kidney transplantation, with no other relevant intercurrents.

At the 23rd gestational week, the patient presented to our emergency department with fever, chills, myalgias, dry cough, dyspnea, pleuritic chest pain, headache, and asthenia associated with COVID-19 infection confirmed 10 days earlier. Her immunosuppression regimen included tacrolimus (6 mg/d), prednisolone (5 mg/d) and AZA (100 mg/d). The latter was discontinued when the infection was diagnosed. She presented with apyrexia, hemodynamic stability (119/52 mm Hg), tachycardia (heart rate: 115 beats per minute), tachypnea (respiratory rate: 24 breaths per minute) and borderline hypoxemia on room air (oxygen saturation of 94% and PaO₂ 66 mm Hg). Bibasal crepitations were evident at pulmonary auscultation. On admission, maternal-fetal examination showed sonographic signs of fetal wellness. Maternal examination revealed lymphopenia ($0.69 \times 10^3/\mu\text{L}$), anemia (10.5 g/dL), and elevated C-reactive protein (121 mg/L). Chest X-ray showed bilateral ground glass opacities. She progressed rapidly with exacerbated hypoxemia and was started on oxygen using a Venturi oxygen mask at 50%, to which she responded appropriately. Due to the increased thrombotic risk associated with COVID-19, prophylactic low-molecular weight heparin was administered, as well as intramuscular betamethasone to promote fetal lung maturation. The good clinical and gasometrical evolution postponed further pharmacological measures. A rapid oxygen weaning was possible, which was discontinued three days after admission and betamethasone initiation. The patient was discharged on day 5, with regular follow-up in the maternal-fetal and transplant clinic. Her tacrolimus levels were within target range, and prednisolone was increased to 10 mg. Accordingly, her low-grade proteinuria was slightly aggravated, with stable levels between 100 and 200 mg/d.

At 28th gestational week, she presented with suspected preeclampsia, with aggravated proteinuria (urine protein/

creatinine ratio > 300 mg/g) and elevated blood pressure. Edema was absent, albumin level was normal and graft function was stable. Fetal well-being was confirmed. Tacrolimus levels were adjusted to higher target levels. She evolved favorably with optimization of antihypertensive therapy and reduction of proteinuria (below 300 g/g). She was discharged on day 13 and followed up regularly at the maternal-fetal clinic and transplant clinic.

At 31 weeks, she was admitted due to oligohydramnios and decreased fetal movements. Anhydramnios developed and the pregnancy was terminated by cesarean section at 33 weeks gestation, delivering a female newborn weighing 2075 g. The newborn is now 15 days old and is suspected to have metabolic disorder, congenital heart defect and mineralizing vasculopathy. The mother was discharged on the 5th day after delivery with regular follow-up at the transplant clinic.

Discussion

In case 1, we consider that both a recent COVID-19 infection and kidney transplantation status may have contributed to the outcome of a cesarean delivery of a growth-restricted neonate. According to the study by Metz et al (April 2021), higher rates of preterm delivery and cesarean section have been described in patients with severe infections than in asymptomatic or mild to moderate infections (11). Fever and hypoxemia (and even elective deliveries) play an important role (11,12). Case 1, like most reports, evolved without hospitalization; therefore, COVID-19 contribution to this scenario may be doubtful. The literature on vertical transmission remains unclear, while placental infection seems infrequent. However, some authors suggest an indirect effect of COVID-19 on the fetus through various mechanisms such as ischemic injury to the placenta (with maternal vascular malperfusion and villitis of unknown etiology occurring even in asymptomatic patients) or an increased inflammatory response due to uncontrolled release of inflammatory cytokines. It leads to significant clinical sequelae, such as preterm birth or fetal growth restriction (12).

In case 2, a somehow rapid progression of COVID-19 infection dictated her first admission. Caution is needed in pregnant woman with COVID-19, as the clinical condition can deteriorate rapidly (2,3). Rinaldi et al described less respiratory failure on admission, however a trend toward higher rates of respiratory failure and higher rates of superinfection in SOT recipients were existed (8). We also believe that the patient has benefited from the use of betamethasone. The latter, along with dexamethasone, is the only agent recommended to induce fetal lung maturity (13). When both fetal lung and maternal treatment are required, dexamethasone might be the first choice,

however distinct steroid regimens have been described too. Recently Berghella and Hughes (14) suggested a modified regimen of bid intravenous (IV) administration of dexamethasone (four doses of 6 mg, twice-daily), followed by 6 mg once daily, oral or IV (for 10 days or until discharge) to continue maternal treatment. Likewise Saad et al recommended a similar regimen of four doses of dexamethasone (but intramuscularly), followed by oral or IV methylprednisolone to complete 10 days of treatment, as a lower fetal steroid exposure has been described (13). Some concerns have been raised about this regimen by Rosen (15) and Mitra et al (16) – should hydrocortisone be used? Are we withholding life-saving treatments with methylprednisolone?

About proteinuria in pregnancy, increases in proteinuria levels can be interpreted as a physiological adaptation to pregnancy (hyperfiltration and reduction in tubular protein reabsorption), but levels above 300 mg/24 hours are abnormal. Nephrotic-range proteinuria (NRP) increases the risk of spontaneous abortion, IUGR and preterm birth. In kidney transplantation, one should seriously consider complications such as preeclampsia (the most common cause of *de novo* NRP in pregnancy), recurrence of the original disease, or chronic allograft nephropathy (17). Proteinuria is also a reported feature of COVID-19; in patients without acute kidney injury, this phenomenon is often transient and of unclear long-term implications (18). Thus, in this patient, there were multiple reasons for elevated proteinuria.

The previously mentioned placental abnormalities are of special interest in this second case (12).

The risk of birth defects in pregnancy post- kidney transplantation is comparable to that of the general population (19). In addition, miscarriages and congenital anomalies do not seem to increase with COVID-19, but data are lacking, especially on the first and second trimesters (20).

Conclusion

There are few, almost none, similar cases reported (1,21). This discussion may raise awareness regarding these complex subgroups where a multidisciplinary approach with a well-trained team of obstetricians and nephrologists is essential to reduce adverse outcomes. It has been more than two years since the SARS-CoV-2 emerged, and so far, we are still facing numerous challenges posed by the ongoing pandemic.

Authors' contribution

AD, AB, DG, SP and LSM were the principal investigators of the study. AD, AB, LSM and JB were included in preparing the concept and design. AB, SP, LSM, and JB revisited the manuscript and critically evaluated the

intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare no competing interests.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patients for publication of this report. Accordingly ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

Funding/Support

None.

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