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CASE REPORT

Cholestasis in pregnancy associated with ciclosporin therapy in renal transplant recipients

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Summary

Obstetric cholestasis (OC) presents with pruritis in the second half of pregnancy and is associated with increased risk of foetal distress, intra-uterine death and premature delivery. From a tertiary referral, renal-obstetric clinic, we report the occurrence of OC in 5/23 pregnancies of women with renal transplants maintained on ciclosporin treatment (European incidence 0.1–1.5% of pregnancies). All required premature delivery for foetal reasons at 33–37/40 (median 34/40). Ciclosporin, at therapeutic concentrations, inhibits bile salt excretion pump (BSEP) function in rats and humans. We propose that OC developed in our patients because the mild inhibition of the canalicular pumps by ciclosporin was only revealed in pregnancy when increases in progesterone metabolites overwhelmed pump function. We suggest that all pregnant women receiving ciclosporin should be closely monitored from the second trimester for the development of OC. If detected, enhanced foetal and maternal monitoring to optimize time of delivery and pregnancy outcome is required.

Introduction

Obstetric cholestasis (OC) usually presents with pruritis in the second half of pregnancy. It is associated with an increased risk of premature birth in up to 60% of cases, foetal distress in 33% and intra-uterine death in 2% [1]. In Europe, the reported incidence varies between 0.1% and 1.5% of pregnancies [1].

In a tertiary referral, obstetric renal clinic, we report the occurrence of OC in five renal transplant recipients under our care taking ciclosporin during pregnancy. During the period of their presentation, we managed a total of 23 pregnancies in renal transplant recipients, thus giving a markedly increased incidence of this serious complication. Women with end-stage renal disease maintained on dialysis have greatly reduced fertility and a functioning renal transplant maybe their best opportunity to achieve a successful pregnancy. Nevertheless, such pregnancies carry an increased risk of hypertension, pre-eclampsia, preterm delivery and intra-uterine growth retardation [2]. Our findings of an increased risk of OC in this patient population may be in keeping with recent progress in the elucidation of genetic factors predisposing to cholestasis.

Results

We report five cases of OC in women with stable renal transplant function maintained on ciclosporin therapy during pregnancy. Their characteristics are summarized in Table 1. Maintenance levels for ciclosporin were trough levels (C0) of 80–120 ng/ml for Neoral and 120–160 ng/ml for Sandimmune. Pruritis occurred at a median of 29 weeks (range: 27–31) and bile acids were elevated in all cases with a median of 31 μM (range: 15–74; normal range: <14). Two patients also had a mild transaminitis and all five were treated with ursodeoxycholic acid at doses ranging from 250 mg b.i.d. to 250 mg q.i.d., with some initial amelioration of symptoms and decrease in bile acid levels in all. However, in two patients bile acid levels or transaminitis deteriorated further at a later stage of pregnancy precipitating delivery. All women had normal levels of serum bilirubin, alkaline phosphatase and

Table 1. Patient characteristics.

Case 1
30 years
End stage renal failure (ESRF) secondary to reflux nephropathy
Cadaveric renal transplant 2 years before conception; mild cellular rejection treated with steroids 18 months post-transplant
Medication at booking: Neoral 100 mg b.i.d., Azathioprine 100 mg o.d., Prednisolone 5 mg o.d., Cephalexin 250 mg nocte
Booking creatinine 136 μm
Creatinine at delivery 178 μm
Creatinine six months postpartum 156 μm
Onset of pruritis 27 weeks
C0 at symptoms 76 ng/ml
Peak bile acid level 31 μm
Delivery at 35/40 weeks for pre-eclampsia and foetal distress
Live girl 3.0 kg

Case 2
33 years
ESRF secondary to focal segmental glomerulosclerosis
Cadaveric renal transplant 7 years before conception; no rejection episodes
Medication at booking: Neoral 187.5 mg b.i.d., Azathioprine 100 mg o.d., Folic acid 5 mg o.d.
Booking creatinine 118 μm
Creatinine at delivery 156 μm
Creatinine 6 months postpartum 134 μm
Onset of pruritis 27 weeks
C0 at symptoms 88 ng/ml
Peak bile acid level 62 μm
Delivery at 34/40 weeks for deteriorating renal function and worsening OC
Live girl 2.3 kg

Case 3
37 years
ESRF cause unknown
Cadaveric renal transplant 4 years before conception; no rejection
Medication at booking: Sandimmune 500 mg o.d., Azathioprine 75 mg o.d., Ferrous sulphate 200 mg t.d.s., Ranitidine 150 mg b.i.d.
Booking creatinine 140 μm
Creatinine at delivery 183 μm
Creatinine 6 months postpartum 147 μm
Onset of pruritis 31 weeks
C0 at symptoms 141 ng/ml
Peak bile acid level 73 μm
Delivery at 33/40 weeks for pre-eclampsia
Live girl 1.8 kg

Case 4
27 years
ESRF secondary to reflux nephropathy
Cadaveric renal transplant 6 months before conception; no rejection
Medication at booking: Sandimmune 300 mg o.d., Azathioprine 100 mg o.d., Ferrous sulphate 200 mg o.d.,
Booking creatinine 82 μm
Creatinine at delivery 83 μm
Onset of pruritis 29 weeks
C0 at symptoms 210 ng/ml
Peak bile acid level 31 μm
Delivery at 37/40 weeks
Live boy 2.8 kg

Case 5
39 years
ESRF secondary to hypertension
Cadaveric renal transplant 11 years before conception; no rejection
Medication at booking:, Neoral 150 mg b.d., Azathioprine 100 mg o.d., Nifedipine LA 60 mg o.d., 1α calcidol 1 μg alt days, Folic acid 5 mg o.d.
Booking creatinine 111 μm
Creatinine at delivery 142 μm
Creatinine 6 months postpartum 138 μm
Onset of pruritis 31 weeks
C0 at symptoms 47 ng/ml
Peak bile acid level 15 μm
Delivery at 37/40 weeks
Live girl 2.7 kg

o.d., once daily; b.i.d., twice daily; t.d.s., three times per day; nocte, at night.

gamma glutaryl transferase and a normal liver ultra-sound scan. There was no association with raised C0 levels and onset of symptoms in these women, but C0 levels often rose after commencement of ursodeoxycholic acid as would be expected because of increased ciclosporin absorption.

All five underwent in-hospital maternal and foetal monitoring and early delivery. Two women developed pre-eclampsia (cases 1 and 3) (Table 1) and one had worsening OC in the presence of deteriorating renal function (case 2). The other two women had elective deliveries at 37 weeks as is our policy in women with OC to prevent late complications such as intra-uterine death. Live births resulted in all cases.

Interestingly, two of the women have had other pregnancies. Case 1 had a pregnancy 10 years prior to transplantation in the presence of chronic kidney disease with no OC. She has also had a more recent pregnancy whilst still maintained on ciclosporin with close monitoring of bile acid levels and development of mild pruritis and a bile acid level of 13 μM (normal range: <14 μM). Case 4 has had a subsequent pregnancy whilst taking Neoral rather than Sandimmune and did not develop OC. Recently, we have routinely monitored bile acid levels in women with renal transplants taking ciclosporin during pregnancy and in three women without symptoms and signs of OC, bile acid levels were not raised.

Discussion

Obstetric cholestasis is likely to be multifactorial in origin with hormonal, genetic and environmental influences.

Disease occurrence predominantly in the third trimester when progesterone concentrations are highest, an increased incidence in twin pregnancies and prompt resolution following delivery all suggest a possible hormonal aetiology. In addition, OC has been reported to be more common in women given additional progesterone therapy to prevent premature delivery [3]. The condition is associated with a significantly raised ratio of 3 α to 3 β hydroxysteroids together with large amounts of mono or disulphated progesterone metabolites excreted in the urine [4]. Under normal circumstances, biliary canalicular transporters are responsible for the excretion of these progesterone metabolites from hepatocytes into bile suggesting a defect in such transporters in OC. Recent progress has been made in the understanding of the genetics of biliary canalicular pumps. Patients with progressive familial intrahepatic cholestasis (PFIC) have been shown to be homozygous for mutations in various biliary canalicular pumps including the bile salt export pump (BSEP) [5] and the canalicular phosphatidlycholine translocase (coded for by the multidrug resistance gene 3 MDR3) [6]. Studies have shown that mothers of patients with PFIC suffered a higher incidence of OC [7] suggesting heterozygosity of such mutations may be a risk factor for disease development. MDR3 mutations lead to greater rises in transaminases, serum bilirubin and bile acids with an accompanying rise in gamma glutaryl transpeptidase (GGT) [8]. GGT does not appear to be elevated in OC caused by mutations in other bile transporters. Thus, mild malfunction of bile canalicular pumps caused by heterozygosity, although causing no problems under normal circumstances, may lead to cholestasis in pregnancy when the system is overwhelmed by the high levels of sex hormones requiring the processing.

Recent studies have addressed the effect of ciclosporin on biliary canalicular transport function. Roman *et al.* [9] using isolated rat hepatocyte couplets, showed that ciclosporin, when used in therapeutic concentrations, caused disorganization of BSEP localization at the canalicular level and functional defects in canalicular vacuole accumulation. This was in contrast to an alternative calcineurin inhibitor, tacrolimus, which had no such deleterious effects. In addition, Byrne *et al.* [10] expressed human BSEP in insect cells and showed that ciclosporin acts as a competitive inhibitor of the pump at therapeutic concentrations. This was confirmed by Horikawa *et al.* [11] who showed that ciclosporin inhibits BSEP and MRP2 (multidrug resistance-related protein 2) in both rat and human canalicular membrane vesicle preparations at inhibition constants similar to clinical concentrations. There is no evidence suggesting that ciclosporin inhibits the function of MDR3 and it is interesting that none of our patients showed a rise in gamma glutaryl transferase and only two had a very mild transaminitis suggesting that ciclosporin was not acting on this transporter.

It is therefore possible to speculate that, much like in the patients with an inherited heterozygosity of canalicular pump dysfunction, cholestasis may become a problem in patients on ciclosporin who become pregnant, because of the competing influences of increased sex hormones needing processing by the canalicular pumps in an environment of relative inhibition of their function by ciclosporin.

The fact that two of these reported women have had pregnancies without OC suggests that it is unlikely that the cholestasis in these women is related purely to their genetic backgrounds and is more likely to be as a result of interplay between relative levels of pregnancy-related hormones and ciclosporin.

Limited evidence suggests that tacrolimus may not have such an effect on canalicular function [9] and be safe to use in pregnancy [12]. If the increased global usage of tacrolimus shows that there are no increased risks of OC, then it may be that tacrolimus would be the immunosuppressant of choice in women with renal transplants who wish to become pregnant and in those who have had clear evidence of OC in a previous gestation with an adverse pregnancy outcome. However, we have shown that OC in women maintained on ciclosporin can be managed safely and given the risks of changing immunosuppressant therapies we would not currently recommend such a policy.

Although there are many published series examining pregnancy in renal transplant recipients, only one mentions OC as a complication. Galdo *et al.* [13] from Santiago report a series of 37 pregnancies in renal transplant recipients in which five women developed OC. However, it is not clear if these women were taking ciclosporin and the authors state that this incidence is not unexpected in their country where OC is generally much more common at 16% [14]. All other series refer to an increase in preterm delivery associated with ciclosporin therapy [2,15–17]. It is possible that in some cases OC was the cause of this complication but not detected as bile acid levels were not recorded. We now monitor bile acid concentrations in all ciclosporin-treated pregnant renal transplant recipients from the second trimester in order to effect prompt management of this condition with ursodeoxycholic acid and enhanced foetal-maternal monitoring to inform optimum timing of delivery.

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