Singapore Journal of Obstetrics and Gynaecology
2009; 40(1): 22-26

Cyclosporine as an Adjunct to Steroids for Idiopathic Nephrotic Syndrome in pregnancy

JM Lee, KH Tan

CASE SUMMARY

Cyclosporine was used as an adjunct to steroids in the management of a case of idiopathic nephrotic syndrome presenting at 27 week gestation in pregnancy. This had allowed the use of low dose steroids to achieve rapid remission of proteinuria with no recurrence whilst avoiding side effects from high dose steroids. There had been no adverse effects on the pregnancy or the fetus, with the pregnancy progressing well to term without any intrauterine growth restriction nor fetal abnormalities.

INTRODUCTION

The use of immunosuppressants is common in women with autoimmune conditions with reproductive potential eg in patients with Rheumatoid arthritis, systemic lupus erythematosus, psoriasis, nephrotic syndrome, Crohn's disease, ulcerative colitis and in organ transplant patients. Some of these patients require high dose steroids for remission which may be detrimental in pregnancy with side effects from high dose steroids and increased risk of gestational diabetes. Other immunosuppressants eg, cyclophosphamide, 6-mercaptopurine and methtrexate have terotogenic effects eg. and cannot be used in pregnancy.

Cyclosporine is a commonly used immunosuppressive agent in organ transplant patients and in various autoimmune conditions as detailed above. It is however classified as a category "C" drug by FDA in pregnancy defined as - risk to fetus not ruled out in human or animal studies but benefits outweigh risks. The extent of placental transfer of cyclosporine is in the range of 37-64% of maternal levels indicating significant amount of drug transfer to the fetus[1]. Except for a meta-analysis on the use of cyclosporine for organ transplant patients in pregnancy[2] (mainly renal transplant patients), there have been few studies on cyclosporine use in pregnancy for autoimmune conditions. Based on the experience from the use of cyclosporine in organ transplant patients[2], there was no evidence of teratogenicity although there was a non significant trend towards an increased risk of pre-term labour and intra-uterine growth restriction. (see discussion section). The dose of cyclosporine used in organ transplant patients is usually 3 to 4 times that used in nephrotic syndrome from primary glomerular disease and other autoimmune conditions.

A search on Pubmed on the use of cyclosporine for nephrotic syndrome in pregnancy did not yield any articles. The use of cyclosporine as an adjunct to steroids in pregnancy for the treatment of nephrotic syndrome in pregnancy has not been studied as steroids alone are usually the mainstay in the treatment of nephrotic syndrome and adjuncts like cyclosporine are generally only used in steroid resistant or frequently relapsing nephrotic syndrome arising from primary glomerular disease. If steroids alone are used, much higher doses and a longer time is needed for remission of nephrotic syndrome. Pregnant patients can ill afford the side effects from prolonged use of high dose steroids (>60mg prednisolone twice a day)

Below is a case report of the successful use of cyclosporine at a dose of 25mg twice a day as an adjunct to steroids in the treatment of idiopathic nephrotic syndrome in pregnancy thus allowing low dose steroid use (prednisolone 30mg once a day) avoiding side effects from high dose steroids and achieving rapid remission of proteinuria with no recurrence. The pregnancy which progressed to term and had no intra-uterine growth restriction.

Dr Lee Jiah Min, MBBS, MRCOG
Registrar
Division of Obstetrics and Gynaecology
KK Women's and Children's Hospital

A/Prof Tan Kok Hian, MBBS, FRCOG, MMed O&G, FAMS
Chaiman Division of Obstetrics and Gynaecology
KK Women's and Children's Hospital

Correspondence to:
Dr Lee Jiah Min
KK Women's and Children's Hospital
Division of Obstetrics and Gynaecology
100 Bukit Timah Road, Singapore 229899
email:dr.jmleel@gmail.com

CASE REPORT

Mdm TSY is a 24 year old primip with Hashimoto's thyroiditis and hypothyroidism for the past 1 year and is currently euthyroid on thyroxine 125ug once a day.

She was followed up antenatally by her private obstetrician at a private hospital and was antenatally well. (Her antenatal bloods were normal, 1st trimester screening was low risk for Down's syndrome 1: 10000, screening scan at 20 weeks showed no fetal abnormalities, and growth was appropriate at 50th% for all 3 parameters.

At 27 weeks of gestation, she had a sudden onset of generalized oedema with bilateral lower limb oedema up to mid thigh level. Her urine albumin was 2+ on dipstick and her 24hr urine albumin was found to be 1.5g per day. Her uric acid level (220 mols/l), liver function tests, platelets and blood pressure (110 / 65 mmHg) were normal making pre-eclampsia an unlikely diagnosis. Urine for microscopy did not show any red cell casts making nephritic syndrome unlikely. Tests for autoimmune antibodies eg anti-nuclear antibody and anti-double stranded DNA were negative. Erythrocyte sedimentation rate was raised, 140mm/hr. Thyroid function tests were normal. Her renal function was normal (serum creatinine was 31mmols/l). Serum glucose was 4.0mmol/l, making diabetic nephropathy unlikely.

She was referred to a renal physician and a diagnosis of idiopathic nephrotic syndrome was made. This was thought to be a new onset of renal disease not related to pregnancy.

The patient decided to be followed up at KK Women's and Children's Hospital (KKH) and was seen at 29 weeks of gestation at our hospital. She was followed up closely by both the obstetrician in KKH and the renal physician and was also referred to the obstetric medical disorders clinic in KKH for monitoring of her thyroid function.

She was started on low dose steroids and cyclosporine - prednisolone 30mg once a day and cyclosporine 25mg twice a day. Diuretics - frusemide 40mg twice a day, together with SpanK 0.6g once a day were given.

Within 3 weeks, her oedema had subsided and proteinuria had decreased significantly from 2+ to nil on urine dipstick (see chart below). As there was a risk of deep vein thrombosis from nephrotic syndrome, the patient was also started on aspirin 100mg once a day.

Her urine microalbumin had decreased significantly, from 1582mg/l to 125mg/l (normal range <250mg/l) in 3 weeks. There was no relapse of nephrotic syndrome while her oral prednisolone dose was being tailed down by 5mg every 2 to 3 weeks. Her cyclosporine dose was maintained at 25mg twice a day. (See chart below)

Table 1. Change in various parameters

Gestation	Normal range	27wks	29wks	30wks	31wks	33wks	36wks	38wks
Urine microalbumin (mg/l)	<250	1582	1102	125	9	5	2	4
Urine creatinine (mmol/l)		1.40	1.10	0.40	0.90	0.80	1.30	1.00
Urine alb/Creatinine ratio (mg/mmol)	3.5-25.0	1130	1001.8	312.5	10.0	6.2	1.5	4.0
Oral prednisolone (mg /day)		30	25	20	15	10	7.5	10
Cyclosporine		---------- Maintained as 25mg bd throughout ----------						
ESR (mm/hr)	<21	140			55		35	

Her serum creatinine and uric acid were normal throughout pregnancy and did not suggest any renal toxicity from cyclosporine. Her blood pressure also remained normal throughout pregnancy.

She was followed up by the obstetric medical disorders clinic in KKH for her hypothyroidism for which thyroxine needed to be increased once at 32 wks.

Table 2. Change in various parameters

Gestation	30 wks	32wks	35 wks
Free T4 (normal range 10.0 to 20.0 pmol/L)	12.5	0.97	14.9
TSH (normal range 0.45 to 4.5 mIU/L)	10.05	10.05	0.319
Thyroxine (mcg om)	125	Increased from 125 to 150	150

Her serum total cholesterol was raised 7.3 (normal <5.2) mmol/l in keeping with the hyperlipidemia associated with nephrotic syndrome.

In view of the possible risk of preterm delivery and intra uterine growth restriction by cyclosporine as suggested by a meta-analysis of cyclosporine use in kidney transplant patients in pregnancy[2] (cyclosporine dose in renal transplant patients are 3 to 4 times higher than that used for nephrotic syndrome), serial growth scans were done 2 to 4 weekly. The fetus however grew well along the 50th for all parameters (head circumference, abdominal circumference and femur length) and the patient had no signs nor symptoms of preterm labour.

Aspirin was stopped at 37 weeks and she delivered at term at 40+0 weeks with a forceps assisted vaginal delivery for prolonged 2nd stage. The baby's birth weight was 3002g, Apgar scores were 9 at one minute and 9 at five minutes. The baby was examined by the neonatologist and was not found to have any abnormalities.

Postnatally, the patient decided not to breastfeed in view of the possible risks of cyclosporine to the fetus as cyclosporine is excreted in the breast milk in small quantities.

She was well when reviewed postnatally at 6 weeks and 3 months and had no relapse of nephrotic syndrome. She is still currently being maintained on cyclosporine 25mg twice a day and low dose prednisolone 10mg once a day and is still on follow up with her renal physician. The baby is also developing well and is achieving normal milestones and growth as assessed by the paediatrician during follow up sessions for baby vaccination.

DISCUSSION

Untreated nephrotic syndrome can lead to spontaneous abortion (3-17%), perinatal loss (5-23%), preterm delivery (9%-35%)[5] and intra-uterine growth restriction. Fetal outcome is usually poorer if associated with impaired renal function or hypertension[5]. A direct relationship between the degree of hypoalbuminemia and low birth weight was reported by Studd and Blainey [6] and Barcelo et al [7].

Steroids are usually the mainstay of treatment of nephrotic syndrome secondary to primary glomerular disease. Adjuncts like cyclosporine, cyclophosphamide or azathiaprine are normally used only in steroid resistant or frequently relapsing nephrotic syndrome. Cyclophosphamide is terotogenic and cannot be used in pregnancy.

In this case, the decision to start the patient on cyclosporine was to achieve a more rapid remission of nephrotic syndrome in pregnancy without the side effects of high dose steroids like increased risk of gestational diabetes, obesity and steroid muscle wasting which a pregnant patient can ill afford. If steroids alone had been used, higher dosages would be required and a longer time needed to achieve remission

Rapid remission from a proteinuria of 1582mg/l per day to 125mg/l per day or urine microalbumin was achieved within 3 weeks in this patient. Prednisolone was tailed down to from 30mg once a day to10mg once a day in 6 weeks, and the side effects from high dose steroids (>60mg twice a day) were avoided.

It is important to have rapid remission of nephrotic syndrome in pregnancy as nephrotic range proteinuria is associated with a hypercoagulable state, causing an increased risk of thromboembolism[4] (deep vein thrombosis, pulmonary embolism) of which the risk is already increased by the pregnant state. Nephrotic range proteinuria also increases the risk of hyperlipidemia[4] and bacteria infections[4] (due to loss of IgG from proteinuria), all of which are normalized when proteinuria stops. Persistently low serum albumin from proteinuria is also associated with intra-uterine growth restriction.[5]

A renal biopsy was not done in this patient as she responded well to cyclosporine. Also, the 3 most common causes of primary glomerular diseases causing nephrotic syndrome (minimal change glomerulonephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis) can all be treated with steroids and alkylating agents like cyclosporine.

A meta-analysis of 15 studies of cyclosporine use in pregnanct renal transplant patients by Bar Oz et al[2] in 1999 showed that the odds ratio of 3.83 for malformations (95%CI 0.75-19.6) did not achieve statistical significance. The overall prevalence of major malformations in the study population (4.1%) also did not vary substantially from that reported in the general population. Odds ratio for prematurity 1.52 (95%CI 1.00-2.32) did not reach statistical significance although the overall prevalence rate was 56.3%. The odds ratio for low birth weight was 1.5 (95%CI 0.95-2.44) . The study concluded that cyclosporine does not appear to be a major human teratogen.

The use of cyclosporine at a dose of 25mg twice a day in this case did not have any adverse effects on intrauterine growth restriction or preterm labour as seen in the meta-analysis of cyclosporine used in renal transplant patients[2]

A possible explanation for the difference in outcome between our case and the results from the meta-analysis could be that in the meta-analysis, only 4 out of 10 studies for pre term delivery and only 1 out of 5 studies for low birth weight were controlled studies, and the results could be skewed by the fact that pregnant patients with renal transplants are high risk in the first place. Poor graft function, hypertension, and elevated serum creatinine prepregnancy have been associated with poorer pregnancy outcomes, such as prematurity and low birth weight. The dose of cyclosporine used for renal transplant patients is usually 3-4 times that used for nephrotic syndrome and other autoimmune conditions; whether there is a dose dependent effect of cyclosporine is not known.

Other than the use of cyclosporine in mainly renal transplant patients, there have been few studies on the use of cyclosporine for autoimmune conditions, connective tissue diseases, nephritic syndrome and dermatologic conditions eg. psoriasis in pregnancy. A search for the "use of cyclosporine for nephrotic syndrome in pregnancy" on Pubmed did not yield any published articles. However, there were anecdotal case reports on the successful use of cyclosporine for other autoimmune conditions in pregnancy[8,9,10,11] like systemic lupus erythematosus, pustular psoriasis and ulcerative colitis which showed disease remission with cyclosporine when high dose steroids had failed. Therewere no apparent fetal side effects like preterm delivery, intrauterine growth restriction nor any fetal abnormalities.

Cyclosporine is a potent systemic immunosuppressant and could potentially be a very useful drug for autoimmune conditions in pregnancy as it allows low dose steroid use with rapid remission of active disease, and is one of the few immunosuppressants that is not teratogenic. More studies are required to confirm this.

Possible side effects to look out for while on cyclosporine are hypertension and renal dysfunction. So far this patient had normal blood pressure and serum creatinine throughout pregnancy.

Contraindications to cyclosporine use include hypertension, renal dysfunction, pre-malignant conditions, active current infection eg with chicken pox[5]. In this case, the patient had none of the above contraindications.

Breast feeding is relatively contraindicated as cyclosporine is excreted in the breast milk at a ratio of 0.17-0.31 to that of maternal serum levels with unknown effects on the baby. However, an anecdotal case report of cyclosporine use throughout pregnancy and 10 months of breast feeding in a woman with a kidney and pancreas transplant found no adverse effects to the infant. At 12 months of age, his weight and height were 46th and 55th centile respectively and he was achieving normal devevelopmental milestones.[12]

CONCLUSION

This case report demonstrates that the use of cyclosporine as an adjunct to low dose steroids is safe and effective for treating nephrotic syndrome in pregnancy, avoiding effects from high dose steroids. There is a need for further studies to confirm this.

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