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REVIEW ARTICLE

Ciclosporin Use During Pregnancy

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Abstract Ciclosporin (cyclosporine) is an immunosuppressive drug first approved for use in organ transplantation to prevent rejection. Ciclosporin is also known to be used for the treatment of psoriasis, rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease, among other indications. While it is recommended that all medications that are not absolutely necessary should be avoided during pregnancy, this may not be an option for many women whose quality of life is significantly impacted without treatment, or for those who must continue immunosuppressive therapy to avoid organ rejection. The purpose of this review is to provide a comprehensive report from the literature of ciclosporin exposure during pregnancy. PubMed, MEDLINE and the Cochrane Database of Systematic Reviews were searched for English-language articles published from 1970 to 2012 that included reports of pregnant women treated at any time during pregnancy with ciclosporin. On an initial search, it was evident that much of the available information is limited to pregnancy after transplant, which suggests that ciclosporin use during pregnancy appears to be associated with premature delivery and low birthweight infants. Comorbidities such as hypertension, pre-eclampsia and gestational diabetes mellitus are also reported at higher incidences than the general population. Medical literature concerning women with autoimmune disorders exposed to ciclosporin during pregnancy are currently limited to case reports and registry data, and, as such, it is difficult to determine if any risks associated with ciclosporin therapy during pregnancy are due to exposure to the drug alone or to pre-existing maternal comorbidities. The literature suggests that ciclosporin therapy during pregnancy should be carefully considered by the treating physician, but may be a safe alternative for patients with autoimmune disease refractory to conventional treatment. Continued monitoring of this patient population remains a key component to understanding the risk factors associated with ciclosporin exposure during pregnancy.

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1 Introduction

Ciclosporin (cyclosporine) is an immunosuppressive drug that has traditionally been used in post-allogenic organ transplantation to help prevent organ rejection. In addition to solid organ transplant prophylaxis, ciclosporin is approved by the US FDA for use in severe psoriasis and rheumatoid arthritis [1]. It has also been used for the treatment of systemic lupus erythematosus (SLE) [2], severe atopic dermatitis [3], pyoderma gangrenosum [4], chronic autoimmune urticaria [5], alopecia [6], aplastic anaemia [7], ulcerative colitis (UC) [8] and Crohn's disease [9] in patients that have not responded to traditional therapies. Additionally, the efficacy of inhaled ciclosporin is

currently being investigated for asthma [10] and chronic rejection of lung transplantation [11], and an ophthalmic solution has come to market for the treatment of keratoconjunctivitis sicca [12]. While the applications of ciclosporin are broad and in many cases essential, questions remain as to the potential risks to both mother and child of taking this immunosuppressant during pregnancy.

Women are 2.7 times more likely than men to acquire autoimmune diseases such as psoriasis, rheumatoid arthritis, SLE and inflammatory bowel disease (IBD), and may require systemic treatment to control their symptoms [13, 14]. While it is recommended that all medications that are not absolutely necessary should be avoided during pregnancy, this may not be an option for many women whose quality of life is significantly impacted without treatment or for those who must continue immunosuppressive therapy to avoid organ rejection. As ciclosporin was first approved for use in transplant prophylaxis, most literature concerning ciclosporin use during pregnancy is limited to transplant data. In fact, medical literature concerning women with autoimmune disorders exposed to ciclosporin during pregnancy is currently limited to scattered case reports and registry data. No comparisons of the reproductive risks in women taking ciclosporin across indications have been made. Subsequently, it has yet to be determined if any increased risk for congenital defects or premature delivery in mothers taking ciclosporin is due to exposure to the drug alone, or due to maternal comorbidities that are often characteristic of transplant patients.

This report is a comprehensive review of all available evidence on pregnancy exposure to ciclosporin, across indications and sources of data. A brief history of ciclosporin and review of pertinent publications on ciclosporin exposure and pregnancy is provided. Data from the National Transplantation Pregnancy Registry (NTPR) for ciclosporin exposure in mothers post-kidney, kidney–pancreas, heart, liver and lung transplant, in addition to the current literature on ciclosporin exposure during pregnancy for all non-transplant indications are reviewed. The aim of this review is to better understand whether the adverse effects of ciclosporin are secondary to the drug, or to maternal illness. We hope to facilitate conversations as to the potential safety or toxicity of ciclosporin use during pregnancy by women that have few alternatives secondary to the severity of their disease process.

2 Methods

2.1 Search Strategy and Criteria

PubMed, MEDLINE and the Cochrane Database of Systematic Reviews were searched for English-language articles published from 1970 to 2012 using the search criteria below. The reference sections of pertinent articles were searched and cross-referenced to the findings from the electronic databases for any additional manuscripts. The following search terms were used either independently or in combination on all three electronic databases: Cyclosporin, Cyclosporine, Neoral, Sandimmune, pregnancy, transplant, psoriasis, autoimmune, toxicity, exposure, organogenesis, congenital defects, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, pharmacokinetics, distribution, adverse effects.

2.2 Inclusion/Exclusion Criteria

Articles were included in the review if the population consisted of pregnant women that were treated at any time during pregnancy with ciclosporin. The records identified from electronic databases were compared with each other and to records from other sources, including references from relevant articles, to identify duplicates. The remaining articles were screened for baseline characteristics of the study population (age, comorbidities, concomitant medications, transplant history), and signs of maternal or fetal ciclosporin toxicity or clinical symptoms. One author assessed each article for inclusion and exclusion criteria, quality as determined by internal validity, and extracted all data. Quality assessment included for randomized, control studies included methods for randomization, blinding, controls and follow-up. Meta-analyses, reviews and observational studies were assessed for measurement bias, confounding items and statistical analysis. Due to the limited data concerning the use of ciclosporin for indications other than transplant, animal models, retrospective cohort studies, case series and reports were also included for this topic.

3 Ciclosporin (Cyclosporine)

3.1 Clinical Pharmacology

Ciclosporin was initially isolated in 1971 from the fungus *Tolypocladium inflatum Gams* and its immunosuppressive effect was discovered in 1976 by employees at Sandoz (now Novartis) (see Table 1 for a list of ciclosporin trade names) [15]. Its primary mechanism of action is to bind to a family of cytoplasmic proteins and form a calcineurin inhibitor complex that effectively halts the proliferation of lymphocytes and the transcription of lymphokines including interleukin-2, tumour necrosis factor (TNF)-α and interferon-γ [16, 17]. Ciclosporin preferentially downregulates T-helper cell function, while having a lesser effect on T-suppressor and cytotoxic cells. In addition, T-cell-

Table 1 Ciclosporin (cyclosporine) formulations and common trade names

Trade name	Pharmaceutical company	Formulation
Sandimmune®	Sandoz/Novartis	Nonaqueous cyclosporine
Cicloral®	Sandoz/Hexal	Generic ciclosporin
Deximune®	Dexcel Pharma	Generic ciclosporin
Neoral®	Novartis	Modified
Gengraf®	Abbott	Modified
SangCya®[a]	Sangstat	Modified
Restasis®	Allergan	Ophthalmic emulsion

[a] Withdrawn from the market

Table 2 Ciclosporin (cyclosporine) drug interactions

Interacting drug class	Mechanism	Potential effect
Azole antifungals	↓ CYP3A4 metabolism	↑ Plasma ciclosporin
Methotrexate	↓ CYP3A4 metabolism	↑ Plasma methotrexate
SSRI	↓ CYP3A4 metabolism	↑ Plasma ciclosporin
HMG-CoA reductase inhibitors (statins)	↓ CYP3A4 metabolism	↑ Plasma ciclosporin
Non-dihydropyridine CCB	↓ CYP3A4 metabolism	↑ Plasma ciclosporin
Losartan	↓ CYP3A4 metabolism	↑ Plasma ciclosporin
Quinine	↓ First-pass metabolism	↑ Plasma ciclosporin
Digoxin	↓ First-pass metabolism	↑ Plasma ciclosporin
Ticlopidine	↑ CYP3A4 metabolism	↓ Plasma ticlopidine
Oxycodone	↓ Gastric emptying and CYP3A4 saturation ↑ Metabolism	↓ Plasma ciclosporin

CCB calcium channel blocker, *CYP* cytochrome P450, *SSRI* selective serotonin reuptake inhibitor, ↑ increase, ↓ decrease

dependent B-cell responses are also inhibited, and, as a result, both cell-mediated and humoral immune responses are muted. This immunosuppressive quality of ciclosporin revolutionized transplant medicine [18].

As an extremely lipophilic peptide, ciclosporin's bioavailability is heavily dependent upon bile salts for efficient uptake and limited by poor oral absorption, first-pass metabolism and enzymatic breakdown at the gut wall [19, 20]. Oral bioavailability has been reported to range from less than 10 % [21] to as high as 89 % and is extensively distributed throughout the body, largely outside of the blood volume [22]. In response to the marked inter- and intra-patient variability in bioavailability, ciclosporin (modified) was designed with a new delivery formulation that would immediately form a microemulsion upon contact with gastrointestinal fluids, making the highly lipophilic ciclosporin less dependent on bile salts for better absorption by the body. The result was more consistent and predictable drug distribution [23].

Ciclosporin is metabolized primarily by the cytochrome P450 3A family of enzymes, which is also responsible for the metabolism of many other drug compounds. Ciclosporin–drug interactions are therefore common and may directly cause fluctuations in ciclosporin concentration, efficacy and toxicity [24]. A list of common agents that interact with ciclosporin is given in Table 2. Elimination follows first-order kinetics, so that a fixed percentage of the drug is metabolized and excreted per unit of time. The largely inactive metabolites are excreted into the bile and a minor amount is eliminated via the urine [25].

The kinetics of ciclosporin may also differ between healthy subjects and transplant recipients, which could be attributed to a number of factors, including confounding drug therapies. In one study of healthy volunteers, the half-life of ciclosporin was 6.2 h [26], which is considerably shorter than the average reported half-life in renal transplant patients of 10.7 h [21].

3.2 Adverse Effects

Ciclosporin-induced nephrotoxicity is an important and clinically significant adverse effect. Acute nephrotoxicity is thought to result from dose-dependent arteriolar vasoconstriction leading to glomerular ischaemia [27]. Chronic ciclosporin-induced nephrotoxicity is thought to be irreversible and is characterized by arteriolar hyalinosis with striped interstitial fibrosis and tubular atrophy [28]. Overall, nephrotoxicity appears to be more prevalent in older patients that take higher initial doses of ciclosporin [29].

Hypertension, secondary to arteriolar vasoconstriction and reflex sodium retention, is also a relatively common reversible adverse effect that does not appear to be dose dependent and has an incidence of approximately 10.6 % for the autoimmune population taking ciclosporin [30], up to 68 % of kidney transplant patients and 44 % of liver transplant patients (Table 3). Confounding comorbidities or duration of therapy may be responsible for the marked difference in incidences. Ciclosporin-related hypertension is managed by dose reduction and antihypertensive medications.

Bacterial, viral and fungal infections are a concern for patients taking immunosuppressive therapy. One large European multicentre study including 265 liver transplant patients taking ciclosporin reported that 71.7 % of patients developed some form of infection while undergoing ciclosporin therapy [31]. US NTPR data reports lower rates for

Table 3 Literature review of pregnancy outcomes for kidney transplant recipients taking ciclosporin (cyclosporine) during pregnancy

Outcomes	NTPR: kidney		NTPR: liver		Ghafari and Sanadgol [61]	Al-Khader et al. [62]	Ghanem et al. [63]
	CsA	Neoral®	CsA	Neoral®			
No. of pregnancies	514	199	96	44	61	113	67
Maternal factors (%)							
Hypertension in pregnancy	62	68	39	44	21	43	19.2
Gestational diabetes mellitus	12	2	2	0	–	21	5.7
Pre-eclampsia	29	28	25	29	26.4	–	–
Infection	23	19	33	33	34	17	13.4
Perinatal outcomes (%)							
Premature (<37 weeks)	52	48	37	28	26.4	64	40.9
Low birthweight (<2,500 g)	46	43	34	41	20.7	–	19.2

CsA ciclosporin, *NTPR* National Transplantation Pregnancy Registry

kidney and liver transplant patients at 23 and 33 %, respectively (Table 3). In contrast, another review of ciclosporin safety data found reported rates of infection in psoriasis patients taking ciclosporin to be 1 % or less [32]. Transplant recipients typically have more comorbidities and are prescribed multiple immunosuppressive drugs. Psoriasis patients may have fewer comorbidities, take fewer immunosuppressants and have hyperactive antimicrobial skin defence, which may help explain this difference.

4 Ciclosporin Exposure in Pregnancy

4.1 Pharmacokinetics

During pregnancy, the body undergoes a number of physiological adaptations to accommodate the growing fetus. Many clinically significant changes may occur that directly affect the absorption, distribution and clearance of ciclosporin.

Gastric emptying and small intestine motility are reduced during pregnancy, which may result in a greater time to absorption and a reduced serum peak ciclosporin level. In addition, nausea and vomiting are a concern for the morning dosing of ciclosporin, when nausea is traditionally more intense early in pregnancy. In the third trimester of pregnancy, plasma volume is increased by 40–50 %, while red cell mass increases only 20–30 %. Total body water increases by approximately 8 litres, and body fat increases by an average of 4 kg [33]. In effect, the volume of distribution and the metabolism of ciclosporin is increased, and ciclosporin trough levels proportionally decrease [34, 35]. It is recommended that immunosuppressive drug levels be monitored more frequently and dosage adjustments may be necessary. Therapeutic levels are attainable; however, postpartum dosages may need to be adjusted as levels increase due to the increase in dosage made during pregnancy.

A case controlled study by First et al. [36] found that ciclosporin dosages were consistently higher in pregnant patients who maintained good graft function than in those who experienced graft dysfunction. The authors concluded that this subpopulation should receive higher ciclosporin doses than the general population, and might benefit from ciclosporin formulations with better absorption [36]. Thus, it could be argued that pregnant mothers taking the unmodified formulation of ciclosporin may benefit from switching to ciclosporin (modified). However, great care must be taken when switching between the two formulations and trough levels should be carefully monitored as multiple factors, as discussed above, contribute to overall ciclosporin blood concentrations. This should only be considered in patients with poor absorption of unmodified ciclosporin, and with strict supervision and collaboration with the managing physician.

4.2 Potential Fetal Exposure

Both the immature fetal liver and placenta can metabolise drugs. The lipophilic nature of ciclosporin allows it to passively diffuse across the placenta and enter the fetal circulation, as noted in one study by Flechner et al. [37], where ciclosporin was detected in the amniotic fluid. However, none was found in an animal study by Sangalli et al. [38] or in another human case report by Lewis et al. [39], which is unsurprising given the lipophilicity of the drug. However, all three studies did find elevated levels in either the placenta and/or cord blood and Lewis et al. [39] reported cord blood ciclosporin to be 62 % of that of the mother's blood at the time of delivery. Venkataramanan et al. [40] found higher concentrations of ciclosporin metabolites in the placenta to be as much as 30 times the concentration of maternal metabolites in fetal cord blood. Sangalli et al. [38] described the distribution of ciclosporin using a model of 12 pregnant rabbits. They reported that

1 % of the drug was found in the central blood compartment, and that the muscle and adipose tissue were the major sites of ciclosporin deposit. The highest concentration of the drug was found in the maternal kidney. The fetus contained less than 0.15 % of the administered ciclosporin, but in contrast to the mother where the kidney was the primary target organ, the fetal liver accumulated the most ciclosporin. Overall, fetal blood accounted for 6 % of the maternal concentration of ciclosporin, and the drug was not detectable in either the maternal or fetal brain [38]. The literature suggests that fetal exposure to ciclosporin is low and non-toxic [41].

Ciclosporin is classified by the FDA as pregnancy risk category "C": that is, although the risk to the fetus has not been ruled out, benefits of use may exceed the risks [42]. Data have shown that the use of calcineurin inhibitors such as ciclosporin during pregnancy does not increase the risk for congenital defects in infants [43, 44]. In 2001, Bar Oz et al. [45] performed a meta-analysis on 15 studies including 410 transplant patients with controls to determine if ciclosporin exposure during pregnancy is associated with an increased risk of congenital malformations, premature delivery or low birth rate. The findings suggested that ciclosporin use during pregnancy is not teratogenic, but may be associated with premature delivery and low birthweight in infants (<2,500 g).

Furthermore, it is known that ciclosporin is excreted in breast milk and the American Association of Pediatrics advises against breastfeeding while taking the drug [46]. One report described the case of a kidney–pancreas transplant patient treated with ciclosporin who chose to exclusively breastfeed her child for 10.5 months. However, although the authors reported a mean breast milk/maternal blood ciclosporin ratio of 84 %, there was no detectable ciclosporin in the infant's blood. They followed the child for a year and noted normal growth and development [47]. Additional articles describing breastfeeding while taking ciclosporin have been published [48–52]. Of the cumulative 15 infants breastfed from the different reports, only one had detectable ciclosporin. The mother discontinued breastfeeding and the infant was healthy and developing well at last follow-up [52]. While any immunosuppressive drug exposure to the infant could potentially exceed the threshold for safety, the relatively small amount of drug transferred and the lack of reported adverse effects together with the documented benefits of breastfeeding may outweigh the theoretical risks of this exposure. Additional studies are warranted.

5 Maternal and Fetal Outcomes Examined

Published articles on the use of ciclosporin in female transplant patients during pregnancy first started to appear in the early 1980s [39, 53]. A few decades later, the number of pregnant women taking ciclosporin for various disorders had significantly increased. With pregnancy registries such as the NTPR and the OTIS (Organization of Teratology Information Specialists) Autoimmune Diseases Study, ciclosporin exposure and its effects on the mother and child can be monitored and studied.

Today, the majority of articles found in the medical literature reporting on the use of ciclosporin during pregnancy are attributed to the field of transplantation; indeed, by 1997, approximately 5,000 pregnancies had been reported in the transplant population [45]. However, since receiving FDA approval for the use of ciclosporin outside of the transplant population, reports of ciclosporin use across all indications have increased in the literature.

5.1 Ciclosporin Exposure in the Transplant Population

When considering pregnancy in the post-transplantation population, a fine balance must be maintained between effective protection against graft rejection and limitation of the toxic adverse effects known to be secondary to immunosuppressive therapy.

Significant experience and knowledge as to the safety of treating pregnant transplant patients with ciclosporin has accumulated. As prospective placebo-controlled trials are unethical, case series and reports, observational cohort studies and pregnancy registries are the currently available resources to accumulate sufficient data to evaluate exposure.

The NTPR was established in 1991 to study the outcomes of pregnancies in female transplant recipients, and as of December 2011 it had enrolled 1,247 female organ transplant recipients with 2,054 pregnancies (Table 4). One meta-analysis by Lamarque et al. [54] gathered data from the NTPR, spontaneous reports, clinical studies and publications. A total of 629 pregnancies in transplant organ recipients treated with ciclosporin were included. Lamarque noted that ciclosporin treatment during pregnancy in transplant patients was associated with the concomitant use of other immunosuppressive agents, antihypertensives and antibacterials, which confounds the clinical picture. The dose of ciclosporin ranged from 1.4 to 14 mg/kg/day, with a mean of 5 mg/kg/day. Fetal losses occurred in 9.7 %, which Lamarque quotes as within the range for the general population. Maternal gestational complications included eclampsia, hypertension, anaemia and diabetes mellitus. Babies were premature, defined as less than 37 weeks, in 44.5 % of cases, and 44.3 % of infants were low birthweight, defined as less than 2,500 g. A total of 3 % of infants had malformations with no particular pattern, which again was in the range of the general population. The authors concluded that there was no evidence for teratogenic effects in humans [54].

Table 4 Number of pregnancies in transplant recipients reported to the National Transplantation Pregnancy Registry (original data as of December 2011)

Organ	Recipients	Pregnancies	Outcomes[a]
Kidney	922	1,490	1,525
Liver	179	319	325
Liver–kidney	5	7	8
Small bowel	2	2	2
Pancreas–kidney	50	90	95
Pancreas alone	2	5	6
Heart	60	105	109
Heart–lung	5	5	5
Lung	22	31	33
Total	1,247	2,054	2,108

[a] Multiple births

Sections 5.1.1–5.1.5 review how the pattern and rate of maternal gestational complications seem to differ with the transplanted organ. However, perinatal complications including prematurity and low birthweight are common to all transplant patients taking ciclosporin during pregnancy.

5.1.1 Kidney Transplant Recipients

Kidney transplant recipients comprise the majority of the literature in post-transplant pregnancy (Table 3). In 2009, the NTPR reported on 713 pregnancies with 737 outcomes, including twins, triplets and quadruplets, to kidney transplant recipients taking either ciclosporin or ciclosporin (modified). Of note is the relatively high rate of maternal comorbidities, including pre-eclampsia, gestational hypertension requiring medical treatment and gestational diabetes, defined by the use of insulin during pregnancy. A comparison of the reported outcomes from the NTPR and other published data is available in Table 3. For the purpose of comparison, in the general population rates of pre-eclampsia, gestational hypertension and diabetes were reported as 6–8, 12 and 1–3 %, respectively.[55, 56] In the small case series presented by the Neoral® Pregnancy Registry for Psoriasis and Rheumatoid Arthritis (NPR; see Sect. 6.1.1), which represents a population with few comorbidities or concomitant medications, there were no reported cases of any of the afore mentioned comorbidities.[57] In addition, prematurity in the general population has been reported to be 9.6 % for singleton births and up to 54 % for twin births [58]. It is important to consider that many kidney transplant patients may be induced prematurely secondary to pre-eclampsia and worsening hypertension. It is unclear whether these comorbidities are secondary to underlying maternal disease or to ciclosporin use necessitating early induction.

Gestational diabetes occurred in only 2 % of the patients taking ciclosporin (modified) as compared with 12 % of patients taking ciclosporin [59]. A 4.9 % occurrence of birth defects in offspring delivered by transplant patients taking ciclosporin was reported. There was no specific pattern of abnormalities noted [60].

Ghafari and Sanadgol [61] reported the outcomes of 61 pregnancies for 53 kidney-transplant patients taking a ciclosporin-based drug regimen during pregnancy. Although they reported a lower rate of gestational hypertension, the rates of pre-eclampsia and infections such as urinary tract infections were still elevated. No cases of gestational diabetes were recorded. Three patients had graft losses as a result of haemorrhagic shock, sepsis and eclampsia. Rates of preterm delivery and low birthweight infants were considerably lower than the data reported by the NTPR, but still higher than the general population. One club foot and one large facial haemangioma occurred in two of the infants. One case of neonatal death was ascribed to prematurity. One mother died due to sepsis [61].

Al-Khader et al. [62] published on 113 pregnancies with ciclosporin exposure post-renal transplant. Gestational hypertension, urinary tract infection and gestational diabetes were also elevated. There was a particularly high incidence of preterm delivery (64 %) [62]. Another retrospective study of 67 pregnancies after renal transplant was published from a single centre in Egypt by Ghanem et al. [63]. They reported 54 of the pregnancies to include exposure to ciclosporin. Gestational diabetes was only mildly elevated relative to the general population. Infection, hypertension and prematurity, however, were more significantly elevated. No episodes of graft rejection were reported. Perinatal mortality was in the order of 9.6 %. The authors concluded pregnancy outcome to be better in the group that was not taking a ciclosporin-based regimen [63].

As supported by Table 3, rates of gestational hypertension and pre-eclampsia are elevated in kidney transplant patients, whose medical history lends itself to hypertension with or without the burden of pregnancy. One study published in 1978, before the approval of ciclosporin therapy for transplant patients in 1983, reported an incidence as high as 49 % for hypertension following renal transplant [64]. After the introduction of ciclosporin, rates of hypertension were reported to be 60–70 % of adult renal and up to 90 % of extra-renal transplant recipients [65]. This suggests that ciclosporin exacerbates hypertension in already prone patients, and as such may be a common finding in pregnancy after transplantation also. The rate of gestational diabetes remains low in this cohort of patients.

Low birthweight often comes hand in hand with prematurity as a complication. Sgro et al. [66] reported on 44 pregnancies post-renal transplant taking some combination of ciclosporin, azathioprine and prednisone, and concluded

that there were significantly more preterm deliveries and low birthweight infants in the transplant group than in controls. Controls were matched for maternal age and smoking status but not medical history/comorbidities. The authors also did not delineate their results based on which participants were taking ciclosporin, azathioprine, prednisone or any combination of the three. All that can be concluded from this study is that there is a higher rate of prematurity and low birthweight infants than in the general population. However, it is still unclear from the literature whether this is due to early induction secondary to maternal comorbidities and fear of graft rejection or whether it is a function of ciclosporin itself.

Overall, although there is a higher incidence of hypertension, pre-eclampsia and prematurity reported, kidney transplant recipients are able to tolerate pregnancy and outcomes are favourable [40].

5.1.2 Kidney–Pancreas Transplant Recipients

The literature on kidney–pancreas transplant patients is limited to a small number of case reports and small series, and NTPR data. One case study described a successful pregnancy in a post pancreas–kidney transplant patient taking ciclosporin and prednisone, with hypertension as the only complication in the third trimester. The baby was born premature (36 weeks) and at a low birthweight (1,900 g) [67]. Another successful pregnancy was reported in a 22-year-old maintained on pre-pregnancy doses of ciclosporin with no maternal complications. The fetus was delivered by elective Caesarean section at 35 weeks after an ultrasound demonstrated decreased fetal growth. Birthweight was 1,690 g. At 9 months the baby was healthy with normal development [68].

A small series described four successful pregnancies after combined pancreas–kidney transplantation in women taking ciclosporin, prednisone and/or azathioprine. In all cases, transplant grafts were stable during pregnancy, and metabolic control was maintained. There was no mention of hypertension or pre-eclampsia. One patient lost pancreas graft function due to an acute rejection after delivery. Of the four outcomes, two were low birthweight, but subsequently showed normal growth and development, and one was born with bilateral cataracts [69]. The incidence of cataracts following ciclosporin exposure was examined in one small animal study that found very high doses (25 mg/kg/day) to induce cataracts in 13 out of 15 rats after 8 months of daily treatment. None of the rats that were given 12.5 mg/kg/day developed cataracts [70].

The NTPR reported data on 43 pregnancies (45 outcomes, two sets of twins) in 31 female kidney–pancreas transplant recipients. There were a total of 36 live births, 22 to patients taking ciclosporin and 23 to patients taking ciclosporin (modified). Patients treated with ciclosporin had a higher incidence of hypertension (95 vs. 82 %), infection (62 vs. 55 %) and rejection episodes (14 vs. 0 %) during pregnancy when compared with the subgroup taking Neoral®. However, graft loss within 2 years of delivery was the same for both groups at 18 %. Prematurity was also higher in the ciclosporin group (83 vs. 65 %) but low birthweight was similar for both groups at around 65 %. At last follow-up all children were reported healthy and developing well; no birth defects were reported. One neonatal death at 26 weeks was reported due to sepsis [71].

Once again, hypertension appears to be the significant reported maternal comorbidity, which is similar to kidney transplant patients. Of interest, however, is the low incidence of insulin use, or gestational diabetes, during pregnancy for pancreas–kidney transplant patients. Prematurity and low birthweight infants were also common findings. Nevertheless, the literature underscores the potential for successful pregnancies after pancreas–kidney transplant for mothers taking ciclosporin.

5.1.3 Liver Transplant Recipients

The 2009 NTPR report included 61 female liver recipients with 96 pregnancies taking ciclosporin and 16 recipients with 44 pregnancies taking ciclosporin (modified). Outcomes are listed in Table 3.

One centre's experience reported 27 pregnancies with exposure to ciclosporin after liver transplantation [72]. There were 21 live births with a median gestation of 37 weeks and mean birthweight of 2,688 g with no congenital abnormalities reported. Pregnancy-induced hypertension was reported in three cases and pre-eclampsia in one.

Successful pregnancies have been reported to the NTPR and in the literature in female liver recipients with exposure to ciclosporin. When compared with kidney transplant recipients (Table 3), pregnancies post-liver transplant had a significantly lower incidence of gestational diabetes, and a lower incidence of hypertension and prematurity, although these complications were still elevated when compared with the general population.

5.1.4 Heart Transplant Recipients

Heart transplant recipients present a unique transplant population secondary to the presence of additional cardiovascular risks associated with pregnancy. Pregnancy-related major haemodynamic changes coupled with significant increases in cardiac output may place the organ at an increased risk of rejection and/or failure as compared with other solid organ transplants.

In 2010, the NTPR reported 42 pregnancies in 23 heart transplant recipients. Of these patients, 22 % had a

rejection episode during pregnancy, which is considerably higher than the 1 and 8 % for kidney and liver recipients, respectively. However, there were no reports of graft loss within 2 years of delivery. Hypertension (52 %) and infection (12 %) were reported at rates similar to other solid organ transplants, and diabetes was reported to be in line with the general population at 2 %. Interestingly, the mean birthweight in these patients overall was among the highest of the transplant populations. The incidence of prematurity and low birthweight was 37 %.

Four infants were reported to have birth defects including facial defects, duodenal atresia, atrioventricular canal defect, tetralogy of Fallot, laryngomalacia and a bicuspid aortic valve. The mothers of these infants had concomitant exposure to mycophenolic acid products during pregnancy [71].

One literature review of 22 published cases of pregnancy after cardiac transplant found an increased incidence of hypertension (36.8 %), infection (27.2 %) and pre-eclampsia (13.6 %). No mention of gestational diabetes was made. Preterm birth was 41.1 and 23.5 % of infants were small for gestational age [73].

Despite the increased haemodynamic burden on the transplanted organ, successful pregnancies after heart transplant have been reported and appear to be tolerated well. In fact, although hypertension and infection were prevalent complications, prematurity and low birthweight infants were reported at lower rates than other transplant recipients.

5.1.5 Lung Transplant Recipients

A series of 32 cases of pregnancy outcomes in female lung transplant recipients on ciclosporin therapy have been described from registry data. There were five therapeutic abortions and 18 live births. Two neonatal deaths were associated with a triplet pregnancy, there was one spontaneous abortion and two deaths after preterm delivery. Seventeen infants were premature and 11 were low birthweight. Sixteen mothers experienced hypertension during pregnancy, seven had infections, seven were diagnosed with gestational diabetes and one mother had pre-eclampsia. Five of the women suffered a graft rejection during pregnancy. No birth defects were reported in the infants [74].

A successful pregnancy after a lung–heart transplant for Eisenmenger's complex was reported in a patient treated with ciclosporin, azathioprine and prednisone. Both mother and child had no gestational or postpartum complications, and the child was born full term at normal birthweight [75].

By comparison with heart recipients, lung recipients have a higher incidence of rejection as well as graft loss in the peripartum period, with smaller newborns. Given the outcomes of alternate transplant site recipients maintained on ciclosporin, it is unlikely that the drug contributes to these increased complications but instead are caused by the maternal comorbidities themselves. This cannot, however, be said with absolute certainty without conduct of a prospective clinical study evaluating lung transplant patients taking ciclosporin head-to-head with alternative graft maintenance medications during pregnancy.

5.2 Fetal Complications in Transplant Patients Taking Ciclosporin During Pregnancy

Although no pattern of birth defects with ciclosporin exposure has been described, there is a consistent association with low birthweight and prematurity. Concern exists that the adverse effects seen in transplant recipients taking ciclosporin for immunosuppression will also develop in the exposed fetus. There has been no clinical evidence of immunosuppression, increased infections or nephrotoxicity in infants of mothers taking ciclosporin during pregnancy, although follow-up in the offspring is, to date, insufficient.

One study investigated the renal function of 12 children older than 1 year born to transplant patients (nine kidney, one pancreas–kidney, one heart, one liver) under ciclosporin maintenance immunosuppression. Inulin clearance, para-aminohippuric acid clearance, microalbuminuria and the electrolyte reabsorption rate were assessed. All 12 children were found to have normal renal function and development despite prolonged in utero exposure [76]. The same investigators that reported on the maternal complications in 113 pregnancies after renal transplant also evaluated the renal function of the same patients' offspring. They concluded that despite ciclosporin exposure throughout the pregnancy and having reduced nephron mass by virtue of their low birthweight, they could not find any glomerular or tubular defects, hypertension or proteinuria in 41 children with a mean age of 52 months [77]. A review of the renal outcome of children exposed to ciclosporin in utero commented that despite the lack of long-term studies in children, there is no evidence of any significant deleterious adverse effect of in utero exposure to ciclosporin [78]. All studies agree that there is a need for longer-term follow-up to rule out any late developing adverse effects to ciclosporin exposure in utero.

Little [79] suggested that immunosuppressant exposure does adversely affect the fetal immune system, if only transiently. Another study, however, evaluated two neonates born to heart–lung transplant recipients. Both ciclosporin and its metabolites were found in the cord blood, but at a lower dose than in the mother. The infants had more T- and B-cells than their mothers, and had similar amounts to cord blood from control infants born to non-immunosuppressed mothers. The authors concluded that neither

infant had a lymphocyte profile suggestive of chronic immunosuppression [80].

Clinical reports note that children of solid-organ recipients develop well, although there is thought that alterations in T-cell subpopulations may affect vaccinations or long-term immunity [81]. A series of 175 newborns of ciclosporin-treated kidney recipients reported to the NTPR showed no evidence of an increased incidence of developmental delays over that expected [82]. Similarly, a study of neurodevelopment in children age 3–15 years exposed to ciclosporin in utero did not show significant differences in full-scale IQ or behavioural outcomes compared with unexposed children [83]. Long-term neurocognitive development of the children of kidney transplant recipients is reassuring considering their high rate of preterm delivery and low birthweight.

6 Ciclosporin Exposure During Pregnancy for Indications Other than Transplantation

The majority of the publications in the medical literature concerning autoimmune disorders in women exposed to ciclosporin during pregnancy are limited to case reports and series, and the outcomes are summarized in Sects. 6.1–6.4 (Table 5).

6.1 Ciclosporin and Psoriasis During Pregnancy

Regarding psoriasis, several studies indicate that a short course of ciclosporin (3–4 months) at a low dose (less than 5 mg/kg/day) results in an 80–90 % improvement in psoriatic disease [84, 85]. One meta-analysis of three major prospective, randomized, parallel-grouped studies in Germany evaluated 579 patients and found dosages less than 5 mg/kg/day to be significantly more effective than etretinate or placebo in the treatment of psoriasis [86]. The Psoriasis Intermittent Short Courses Efficacy of Sandimmun (PISCES) group conducted a 1-year randomized trial of 400 patients with psoriasis. From their findings they recommended intermittent short-course ciclosporin therapy in conjunction with a topical therapy [87, 88].

The low dosage combined with the short bursts of ciclosporin usage render the psoriatic population less susceptible to adverse effects. This population of patients also lacks the comorbidities and concomitant medications inherent to the transplant population. In short, many of the safety concerns that are seen in long-term, high-dose usage may not apply to psoriasis patients, especially during pregnancy. More importantly, the relative lack of comorbidities and multi-drug regimens in this patient population may help to clarify the safety profile of ciclosporin use during pregnancy.

A number of recent case reports demonstrate the efficacy of ciclosporin use during pregnancy to control severe psoriasis [89–94]. No incidence of maternal complications was reported, although prematurity and/or low birthweight were common. With the exception of one case report, all of the mothers were started on low-dose ciclosporin during the pregnancy and were often weaned off before delivery. In only one report did the patient receive ciclosporin preconception and maintain treatment throughout the pregnancy. There were no complications for mother or child [95].

Table 5 Overview of literature concerning pregnancy outcomes in women using ciclosporin (cyclosporine) during pregnancy for indications other than transplant

Disease	No. of patients	Age (years)	Additional medications	Known comorbidities	Pregnancy outcome (%)	Premature birth (%)	Low birthweight (%)
Psoriasis [89–94, 97]	19	20–38	High-dose prednisone (5)	Smoker and chronic inflammatory disease (1); MS and recurrent spontaneous abortions	95	21	21
SLE [43, 98–103]	18	28–32	All prednisone; hydroxychloroquine, IV immunoglobulin (1); immunoadsorption therapy (1)	Lupus nephritis (1), polymyositis (1)	94	22	22
IBD [105, 108–110]	5	21–36	Prednisolone (2); azathioprine, thioguanine, mesalamine, sertraline (1)	Not available	100	100	80
Other[a]	5	26–30	Not available	Not available	100	60	80

IBD inflammatory bowel disease, *IV* intravenous, *MS* multiple sclerosis, *SLE* systemic lupus erythematosus

[a] Aplastic anaemia (2) [116, 117], impetigo herpetiformis (2) [118, 119], systemic sclerosis (1) [120], hemophagocytic lymphohistiocytosis (1) [121]

The National Psoriasis Foundation Medical Board recommends that of the oral medications approved for psoriasis, only ciclosporin should be considered during pregnancy [96]. They note that due to the unique immunological state of the pregnant mother, psoriasis often improves during pregnancy [96]. However, if it is debilitating, ciclosporin can be used with sufficient counselling to the patient.

6.1.1 The Neoral® Pregnancy Registry

The NPR [97] was established in 1999 to gather information to determine the safety of Neoral® use during pregnancy in this patient population (Table 6). All of the patients enrolled in the registry suffered from symptoms of severe psoriasis necessitating treatment with Neoral® during pregnancy. To date, no patients with rheumatoid arthritis have been enrolled. In this patient population taking Neoral® (ciclosporin, modified) during pregnancy, so far there have been no reports of prematurity or low birthweight infants. The most frequently reported maternal complication was urinary tract infection (36 %), and there were no reports of gestational hypertension, diabetes or pre-eclampsia. Mean gestational age was 39.9 weeks and mean birthweight was 3,516.7 ± 518.1 g. One infant was born with ventral penile chordee and an incomplete dorsal hooded foreskin with no evidence of hypospadias, which was corrected with minor surgery. No other birth defects were reported.

The data from the NPR includes a small cohort of participants but reinforces the lack of maternal complications, with the exception of infection, in mothers taking ciclosporin during pregnancy. However, the lack of preterm delivery in this cohort is at odds with much of the, granted very limited, data to date in this population.

In conclusion, the available reports suggest that the increased incidence of maternal comorbidities during pregnancy reported in transplant recipients are due to the disease process itself, and not to ciclosporin use. Or it may be that transplant recipients are on higher doses of ciclosporin for longer, and thus exhibit ciclosporin toxicity through these complications. What can be concluded from the psoriasis data, however, is that the isolated use of ciclosporin in otherwise healthy women during pregnancy is safe, understanding that there may be a risk for preterm delivery with low birthweight infants.

Table 6 Summary of pregnancy outcomes for psoriasis patients enrolled in the Neoral® Pregnancy Registry [57]

Outcomes	Psoriasis patients
No. of patients	11
Therapeutic abortions (%)	0
Spontaneous abortions (%)	0
Ectopic pregnancy [no. (%)]	1 (9)
Stillborn (%)	0
Live births [no. (%)]	10 (90)
Mean gestational age (weeks)	40 ± 0.8
Premature (<37 weeks) [%]	0
Mean birthweight (g)	3,517 ± 518
Low birthweight (<2,500 g) [%]	0

6.2 Ciclosporin and Systemic Lupus Erythematosus During Pregnancy

Although not FDA approved for this indication, ciclosporin's selective and reversible inhibition of T-cell-mediated responses may be a desirable alternative to the traditional corticosteroid therapeutic options that cause a global immunological inhibition and associated adverse effects in SLE patients. Limited reports exist for ciclosporin use in SLE during pregnancy.

In one single-centre experience, Østensen et al. [43] reported 49 pregnancies in women with a variety of autoimmune diseases who were exposed to a number of biological agents and immunosuppressive drugs during pregnancy. Of these 49 pregnancies, 14 were exposed to ciclosporin (13 throughout the entire pregnancy, one discontinued in the second trimester). Ten women had SLE, two primary Sjögren's syndrome and two psoriatic arthritis. Pregnancy outcomes included one miscarriage and 12 live births, with five premature deliveries. One premature infant presented with multiple abnormalities and died. The authors state that the majority of premature deliveries occurred in patients suffering from SLE, regardless of the therapy used [43].

Another study evaluated the influence of fetal exposure to immunosuppressive drugs (ciclosporin, azathioprine and dexamethasone) used during pregnancy in women with autoimmune diseases. Five out of ten mothers received ciclosporin for a mean duration of 206 days during pregnancy, and three of these five women had SLE. Complete blood counts were in the normal ranges for all offspring except one that was exposed to ciclosporin in utero. The infant presented with neutropenia, which resolved within the first year of life. Another infant exposed to ciclosporin in utero presented with low levels of all of the immunoglobulin isotypes. No statistically significant differences were observed between the exposed and non-exposed infants [98].

One study enrolled 16 women with SLE undergoing ciclosporin treatment: three of these women became pregnant and two chose to discontinue therapy. Only one chose to remain on ciclosporin throughout the pregnancy; she had an uncomplicated pregnancy and gave birth to a

healthy infant [99]. Additional case reports of individual pregnancies of SLE patients with ongoing ciclosporin therapy are notable for the lack of reported maternal complications or birth defects. One of four reported patients delivered prematurely and one gave birth to an infant of low birthweight [100–102]. Another case report describes a woman suffering from SLE and polymyositis who was prescribed ciclosporin at 6 weeks' gestation as part of the treatment regimen along with prednisone, hydroxylchloroquine and six cycles of high-dose intravenous immunoglobulin. The patient delivered a low birthweight (1,800 g) infant at 33 weeks' gestation after pre-term rupture of the membrane. At 15 months' follow-up, the child's height and bodyweight were above the 25th percentile and a neurodevelopment assessment was normal [103].

Table 5 summarizes the outcomes described above for prematurity and birthweight. It appears that while the incidence of prematurity is still higher than that of the general population, it remains significantly lower than the transplant population. Of note is the total lack of maternal complications during pregnancy such as hypertension, diabetes and pre-eclampsia. However, the sample size is too small to draw any definitive conclusions.

6.3 Ciclosporin and Inflammatory Bowel Disease During Pregnancy

The literature on ciclosporin usage during pregnancy for IBD is limited. The association of ciclosporin with prematurity and intrauterine growth restriction leads clinicians to administer it only in severe cases when fulminant colitis in pregnancy fails to respond to a corticosteroid regimen [104].

Ciclosporin has, however, been used to prevent miscarriage resulting from flares of UC during pregnancy. Ciclosporin was administered to a 21-year-old primigravida that failed to respond to corticosteroid therapy for a fulminant flare of UC at 13 weeks' gestation. The pregnancy was prolonged to 29 weeks, which was attributed to the remission induced by ciclosporin. An acute colectomy was also avoided in this patient, which would have been a significant risk to both mother and child [105]. One study that included five IBD patients taking ciclosporin during pregnancy concluded that ciclosporin was effective for the induction of remission of colitis, but should only be used in severely ill patients. The investigators noted that severe relapses of colitis that are inadequately treated during pregnancy can alone increase the risk of prematurity and low birthweight [106].

A retrospective study on 113 pregnancies with 207 outcomes was conducted in patients suffering from IBD during pregnancy. Of the 113 patients, two were treated with ciclosporin. No specific pregnancy data were reported for the two patients; overall, the study concluded the drugs used for the treatment of IBD did not appear to be associated with poor pregnancy outcomes and there were similar complication rates to the general population [107].

Two cases were reported by Reindl et al. [108]. The first patient was a 31-year-old that developed an acute UC flare during her first pregnancy and was treated with ciclosporin, which was later discontinued secondary to hypertrichosis. She gave birth at 36 weeks' gestation to a healthy infant. The second patient was a 34-year-old that presented at 13 weeks' gestation with an acute flare that failed to respond to conventional treatment. The patient received ciclosporin therapy for 8 weeks, during which she presented with one episode of second-degree arteriovenous block and developed hypertrichosis. In the 25th week of pregnancy, the patient had an emergency Caesarean section for suspected placental insufficiency. The infant suffered from respiratory distress syndrome, a fracture to the femur and a third-degree intracerebral haemorrhage. Follow-up showed normal motor skill and intellectual development of the child [108]. Another report presents the case of a woman started on ciclosporin in her 29th week of pregnancy, and discontinued 6 weeks postpartum secondary to hypertrichosis. The infant was healthy but premature with a low birthweight [109]. Finally, a 36-year-old woman with corticosteroid-resistant UC was started on ciclosporin (2 mg/kg) during her 23rd week of pregnancy with symptomatic improvement. She underwent an emergency Caesarean section at 35 weeks due to an antepartum haemorrhage. The offspring was healthy, although premature and subsequently low birthweight [110].

A number of review articles have individually evaluated the safety of immunomodulator use during pregnancy for the treatment of irritable bowel syndrome and IBD [111–114]. They each conclude that while ciclosporin is not teratogenic, it may still be toxic to mothers and potentially cause hypertension, nephrotoxicity and hepatotoxicity. All are in agreement that its use should be reserved for corticosteroid refractory disease, and as an alternative to emergent surgery in UC.

Case reports on the use of ciclosporin during pregnancy for women suffering from IBD are inherently skewed toward prematurity and low birthweight, and so should not be used in the risk analysis for this complication. Ciclosporin use in IBD is reserved for disease refractory to other treatments and for women with disease severe enough to itself threaten miscarriage and preterm labour. Of note is that several authors attributed disease remission and prolonged pregnancy to the use of ciclosporin, and that no additional maternal complications such as hypertension, pre-eclampsia and hypertension were noted.

6.4 Ciclosporin and Other Indications During Pregnancy

The efficacy of ciclosporin in treating refractory rheumatoid arthritis is well established; in 1997, the FDA approved the use of ciclosporin for severe, active rheumatoid arthritis where the disease could not be adequately controlled with methotrexate. Many biological agents have been approved for the treatment of rheumatoid arthritis, including TNF inhibitors, which selectively target the immune system. These agents, while effective, are not well studied during pregnancy and pregnancy outcome data are not available.

In a review of the literature of the different treatment modalities during pregnancy for patients with rheumatoid arthritis, the risks and outcomes of ciclosporin were reported to be well studied. The investigators stated that it can be used throughout pregnancy and found that doses of 2–3.5 mg/kg/day do not increase the risk of prematurity or low birthweight [115].

Due to the success of ciclosporin treatment in transplant and autoimmune patients, ciclosporin has been used in trials for many conditions that may benefit from some element of immunosuppression. Reports of its off-label use in general are limited, and reports of its off-label use during pregnancy are even more infrequent. There are, however, some case series and reports that highlight some potential uses of ciclosporin during pregnancy outside of its known indications.

In one case series, ten women with pregnancy-induced aplastic anaemia were treated with ciclosporin antenatally, with a partial response noted in one. One offspring whose mother was given ciclosporin antenatally had jejunal atresia at birth [116]. Also, one 29-year-old patient was started on ciclosporin treatment for idiopathic aplastic anaemia prior to conception and remained on ciclosporin for the duration of the pregnancy. At 37 weeks she developed hypertension. At 38 weeks, the patient gave birth to a healthy infant weighing 2,150 g [117].

Two case studies report the successful use of ciclosporin in treating corticosteroid-refractory impetigo herpetiformis, a severe form of pustular psoriasis during pregnancy. One infant was premature and low birthweight, but both were healthy with no birth defects [118, 119]. Basso et al. [120] reported on a successful pregnancy in a 29-year-old with systemic sclerosis treated with ciclosporin. A healthy infant was born via Caesarean section at 34 weeks with a low birthweight.

Yamaguchi et al. [121] reported a case of a patient in her second trimester who was diagnosed with hemophagocytic lymphohistiocytosis associated with herpes simplex virus-2 infection. She was unresponsive to corticosteroid treatment, although she responded to ciclosporin treatment and delivered a full-term infant with normal birthweight and no abnormalities.

The data for off-label use of ciclosporin for autoimmune disease is difficult to interpret as the sample sizes for each disease process are low, there is no standardization as to what complications are reported, and many of the conditions are exceedingly rare, so data on the baseline prevalence of maternal complications during pregnancy for this cohort are insufficient. However, prematurity and low birthweight infants in this cohort continue to be reported.

7 Summary and Conclusions

Every year, the number of women taking immunosuppressive therapy after transplantation or for autoimmune disease increases steadily. Ciclosporin has been available for more than 30 years and its mechanism, pharmacokinetics and side effect profile are now well characterized. Ciclosporin crosses the placenta and so the question of maternal and fetal safety during pregnancy is raised.

As ciclosporin was initially used as a successful therapy against organ rejection, the transplant literature was the first to describe ciclosporin use during pregnancy. Transplant patients are maintained on multiple drug regimens and have a number of comorbidities and complications unique to their population, which further complicate analyses. Overall, based on case, centre and registry reports, ciclosporin exposure during pregnancy in the transplant population does not appear to be associated with an increased risk of congenital malformations. However, ciclosporin use does appear to be associated with premature delivery and low birthweight infants, but no reports distinguish between mothers that are induced prematurely to minimize the burden of pregnancy on the transplanted organ, or those that go naturally into preterm labour or are induced secondary to a maternal comorbidity or complication of ciclosporin use. Furthermore, comorbidities such as drug-related hypertension, pre-eclampsia and gestational diabetes are reported at higher incidences than the general population but also appear to be organ specific. Kidney transplant recipients may be at the highest risk of developing gestational hypertension, as hypertension is a common complication of the transplanted organ itself, secondary to renin–angiotensin dysregulation and renal artery stenosis, to name a few. As hypertension is part of the criteria for pre-eclampsia, a concomitant increase in the incidence of this reported complication is unsurprising. The trend for all types of transplant recipients is, however, towards hypertension, which may be due either to the maternal disease process itself or ciclosporin, or a combination of factors. Gestational diabetes does not appear to be a significant risk with the use of ciclosporin during

pregnancy. Rates of infection, however, are expected to rise with any immunosuppression use.

The literature regarding ciclosporin exposure during pregnancy for patients with autoimmune disorders is limited to case reports and case series, the small study populations of which prevent generalized conclusions. Psoriasis as an indication for ciclosporin use may provide the clearest picture as to the safety profile for ciclosporin use in pregnancy, as these patients tend to have few maternal comorbidities and rarely take concomitant medications. Patients with IBD, however, are not good candidates for comparison due to the necessary severity of their disease process before ciclosporin management is considered, and due to their underlying risk for premature labour [106]. However, it is clear that maternal complications such as gestational hypertension, diabetes and pre-eclampsia are not reported with any frequency in patients with autoimmune disease taking ciclosporin during pregnancy. This suggests that short-term, low-dose use of ciclosporin surrounding pregnancy is safe and should be considered for patients with severe disease refractory to first-line medications. Additionally, despite higher incidences of maternal complications, ciclosporin use during pregnancy for transplant recipients appears to be well tolerated with thousands of reported births as testament.

Overall, the literature reports a lower mean gestational age and mean birthweight for women exposed to ciclosporin during pregnancy across all indications than in the general population. However, it is not clear if the maternal complications are related to ciclosporin exposure during pregnancy or to maternal disease. Alternatively, data from the NPR show that ciclosporin exposure during pregnancy in women with psoriasis does not appear to have a detrimental effect on gestational age or infant birthweight. This may suggest that maternal comorbidities and multiple drug regimens are responsible for this trend. More likely, it infers that a short burst of ciclosporin use surrounding and during pregnancy in an otherwise healthy woman is safe for both mother and child. No specific pattern of structural malformations has been reported and infant development appears to be normal with no complications, although the data remain limited.

In conclusion, ciclosporin use during pregnancy may be a safe alternative for patients with autoimmune disease refractory to conventional treatment. Continued monitoring of this patient population remains a key component to understanding the risk factors associated with ciclosporin exposure during pregnancy.

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Neoral® Pregnancy Registry for Psoriasis and Rheumatoid Arthritis To contact the NPR to report additional pregnancies: Gift of Life Institute, 401 N. 3rd Street, Philadelphia, PA 19123, USA; Phone: Toll-free 001-888-522-5581; Email: npr.registry@giftoflifeinstitute.org; Website: http://www.npr.giftoflifeinstitute.org

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