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Immunological Status of Children Born to Female Liver Recipients

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Background: Immunosuppressive treatment in pregnant organ recipients can affect functions of the fetal and newborn immune system. The aim of this study was to evaluate the effect of this treatment on selected parameters of the immune system of children born to mothers after liver transplantation.

Material/Methods: The study included 52 children born to liver recipients and 52 children in the control group. The study was conducted in the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. Children from the 1st day of life to 10 years of age were examined. Serum antibody concentrations of IgG, IgM, and IgA were measured by the immune agglutination method on a Cobas 6000 analyzer.

Results: Comparison of mean IgG, IgM, and IgA levels and with reference values did not show a significant difference between the study and control group ($p>0.05$). Immunoglobulin concentrations were also analyzed in the groups of children according to their age at the time of the test and the type of calcineurin inhibitor used in the mother's treatment. The analysis showed a significant difference in the distribution of IgA concentrations in comparison to the normal values ($p<0.05$), as well as mean IgA ($p<0.05$) and IgM concentrations ($p<0.05$) according to the type of immunosuppressive treatment of the mother (tacrolimus or cyclosporin treatment regimen).

Conclusions: Analysis of the type of immunosuppressive therapy used during pregnancy revealed a possible influence of the type of calcineurin inhibitor on selected parameters of the immune system of the children; however, further research is needed to confirm these findings.

MeSH Keywords: **Child • Immune System • Immunosuppressive Agents • Liver Transplantation • Pregnancy**

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Background

Since the first successful transplantation in 1954, there has been a dynamic development of clinical transplantology and immunosuppressive therapy. In women, organ insufficiency preceding transplantation leads to menstrual disorders and infertility, but the level of medical knowledge now has increased the chance of these women to have children. Several months after transplantation, reproductive ability is restored [1]. The optimal time for conception after transplantation is 2 years, although some sources say that it is possible to shorten this time to 1 year [1].

The immunosuppressive agents most commonly used by patients after organ transplantation are tacrolimus, cyclosporine, azathioprine, glucocorticoids, mycophenolate mofetil, everolimus, and sirolimus. The main drugs used in the treatment regimens are calcineurin inhibitors: tacrolimus or cyclosporine [2]. Most of these drugs have been classified as Category C according to the FDA (Food and Drug Administration). These drugs pass through the placenta and can have a negative effect on the fetus, including lymphatic system damage, but the literature on this problem is still scarce [2–6].

The immune system evolved to protect the body against infections. Despite some differences among adults, children, and newborns, protection of the newborn against infection is sufficient if the mother's condition was good, the duration and the method of pregnancy termination were adequate, and the newborn was breastfed after delivery, but this rarely happens in children born to mothers after organ transplantation.

One of the main tests that may be used to assess the immune system is serum immunoglobulin (IgG, IgM, IgA) levels [7]. Recurrent bacterial infections are manifestations of antibody deficiencies. In congenital immune deficiencies, infections typically occur between about 4 and 6 months of life, which is when maternal IgG disappears [8]. Slow physiological development of the immune system in children results in the normal values of immunoglobulin levels in the blood that vary depending on the age of the child [7].

Aim

The aim of this study was to evaluate the effect of different types of immunosuppressive therapy on selected immune system parameters in children born to mothers after liver transplantation.

Material and Methods

The study group (LT) consisted of 52 children born to mothers after liver transplantation, aged between 1 and 10 years, born between December 2001 and July 2013, and examined in the period between December 2010 and July 2013, in the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. The control group involved 52 children born between March 2001 and July 2013, at similar gestational ages as the children in the study group, whose mothers consented to participate in the study.

Tabel 1. Characteristics of children from the study and control group.

	LT		LT-control	
Age on the examination day (days)				
Minimum	1		1	
Maximum	3445		3648	
Mean	1017		1046	
SD	985		1009	
Number of children in age groups				
	n	%	n	%
Newborns	16	30.8	14	26.9
Infants	5	9.6	6	11.5
Children >1year	31	59.6	32	61.6
Weight (g)				
Minimum	1320		1278	
Maximum	4100		4720	
Mean	2899		3064	
SD	596		715	
Weeks of gestation				
Minimum	30		30	
Maximum	41		41	
Mean	36.8		37.25	
SD	2.1		2.4	
Type of pregnancy termination				
	n	%	n	%
Vaginal delivery	15	28.8	35	67.3
Cesarean section	37	71.2	17	32.7
Immunosuppressive regimen in mother				
	n	%	n	%
Tacrolimus-based	41	78.9	0	0
Cyclosporine-based	11	21.1	0	0

LT – children born to mothers after liver transplantation; LT-control – control group.

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Table 2. Reference values for immunoglobulin concentrations according to the age of children developed by Wolska-Kuśnierz B. [8].

Age	IgG [g/l]	IgA [g/l]	IgM [g/l]
1–7 days	9.04 (6.33–11.6)	0.06 (<0.06–0.06)	0.092 (0.045–0.21)
8–days–2 months	5.95 (3.36–10.50)	0.062 (<0.06–0.07)	0.28 (0.21–0.51)
3–5 months	2.97 (1.93–5.32)	0.13 (<0.06–0.77)	0.38 (0.23–0.69)
6–9 months	3.24 (1.97–6.71)	0.16 (0.065–0.52)	0.43 (0.21–0.89)
10–15 months	4.20 (2.19–7.56)	0.17 (0.07–0.45)	0.47 (0.21–1.04)
16–24 months	6.27 (3.62–12.20)	0.31 (0.13–0.93)	0.68 (0.39–1.54)
2 1/12–5 years	7.55 (4.38–12.3)	0.54 (0.10–1.33)	0.67 (0.30–1.12)
5 1/12–10 years	11.11 (8.53–14.40)	1.06 (0.38–2.35)	0.71 (0.36–1.98)
10 1/12–14 years	11.31 (7.08–14.40)	1.22 (0.62–2.30)	0.90 (0.50–2.13)
14 1/12–18 years	10.82 (7.06–14.40)	1.19 (0.85–1.94)	0.76 (0.44–1.13)

Immunosuppressive drugs used by mothers in the study group were tacrolimus, cyclosporine, glucocorticosteroid, and azathioprine. The characteristics of children in the study and control group included their age at the time of examination, gestational age, birth weight, and the type of termination of pregnancy (Table 1).

All mothers of the examined children signed consent for participation in the study, and the study protocol was approved by the Bioethics Committee of the Medical University of Warsaw (KB/174/2009). The research funded by a grant (No. N N407 534938) from the Ministry of Science and Higher Education.

To assess immunity, antibody IgG, IgM, and IgA levels were used. Venous blood samples were taken during a visit to the clinic. After clotting and centrifugation, immunoglobulin IgG, IgM, and IgA concentrations were determined by the immunoturbidimetric method on a Cobas 6000 (Roche) analyzer. The tests were done at the Central Laboratory of the Hospital of Baby Jesus in Warsaw.

To evaluate antibodies, concentration reference values for immunoglobulin concentrations according to the age of children developed by Wolska-Kuśnierz et al. were used (Table 2) [7].

Beside the comparison of the results with respect to the normal value, the mean concentrations of particular immunoglobulins were compared. To compile the collected data, descriptive methods and statistical reasoning methods were used. The chi-square test was used to compare the incidence of individual variants in the studied groups and subgroups and to examine the relationship between the qualitative variables. In the case of small numbers in some fields of the tables, Yates' correction was used for calculate chi-square analysis.

Before comparing the mean of the measurable variables, the compatibility of their distributions with the normal distribution was checked using the Shapiro-Wolf compatibility test. For the comparison of 2 independent trials, the Mann-Whitney test was used.

Statistically significant values were the differences between the means (or frequencies) and variables for which the calculated test value was equal to or greater than the critical value read from the corresponding tables with the number of degrees of freedom and the probability of error <0.05. The statistic calculations were based on STATISTICA 10 software.

Results

The following table shows the results of IgG, IgM, and IgA levels and the number of children (n) who had results above the normal value, normal, and below the normal value for age, as well as mean concentrations of immunoglobulins in the study and control group, and in groups extracted according to the age of children at the time of study or the regimen of immunosuppressive therapy administered to the mother (Table 3).

There were no statistically significant differences in the IgG, IgM, and IgA concentrations between the study group and control group ($p>0.05$). The comparison of mean IgG, IgM, and IgA concentrations in the analyzed groups also showed no statistically significant differences ($p>0.05$).

IgG, IgM, and IgA immunoglobulin concentrations were also analyzed in the groups of children separated according to the age of children at the time of the study. Children were divided into 3 groups: newborns (1 to 28 days), infants (>28 days

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Table 3. Distribution of results in relation to norms and mean IgG, IgM, and IgA in the study and control group, in the groups extracted according to the age of children at the time of the study, and according to the mother's immunosuppressive regimen.

Age		IgG				IgM				IgA			
		LT		LT-control		LT		LT-control		LT		LT-control	
		n	%	n	%	n	%	n	%	n	%	n	%
Newborns	↑	3	18.7	3	14.3	0	0	0	0	0	0	0	3.6
	N	13	81.3	9	64.4	3	18.7	3	21.4	16	100.0	14	96.4
	↓	0	0	2	14.3	13	81.3	11	78.6	0	0	0	0
	Medium [g/l]	9.312±2.09		9.143±2.48		0.025±0.06		0.05±0.09		0.0±0.0		0.0±0.0	
Infants	↑	1	20.0	0	0	1	20.0	1	16.7	0	0	0	0
	N	4	80.0	6	100.0	1	20.0	2	33.3	2	40.0	3	50.0
	↓	0	0	0	0	3	60.0	3	50.0	3	60.0	3	50.0
	Medium [g/l]	5.0±1.58		4.667±1.03		0.4±0.55		0.5±0.55		0.0±0.0		0.0±0.0	
Children >1 year	↑	4	12.9	2	6.3	5	16.1	4	12.5	3	9.7	5	10.7
	N	25	80.6	28	87.4	25	80.7	26	81.3	17	54.8	17	62.5
	↓	2	6.5	2	6.3	1	3.2	2	6.2	11	35.5	10	26.8
	Medium [g/l]	9.677±2.99		9.188±2.38		1.129±0.43		1.063±0.44		0.838±0.73		0.938±0.88	
All age groups	↑	8	15.4	5	9.6	6	11.5	5	9.6	3	5.8	5	9.6
	N	42	80.8	43	82.7	29	55.8	31	59.6	35	67.3	34	65.4
	↓	2	3.8	4	7.7	17	32.3	16	30.8	14	26.9	13	25.0
	Medium [g/l]	9.12		8.65		0.717		0.725		0.500		0.577	
Tacrolimus regimen	↑	6	14.6			3	7.3			0	0		
	N	34	82.9			23	56.1			29	70.7		
	↓	1	2.4			15	36.6			12	29.3		
	Medium [g/l]	9.415				0.693				0.39			
Cyclosporin regimen	↑	2	18.2			3	27.3			3	27.3		
	N	8	72.7			6	54.5			6	54.5		
	↓	1	9.1			2	18.2			2	18.2		
	Medium [g/l]	8.0				0.818				0.909			

↑ – above norm value; ↓ – below norm value; N – normal; n – numer of children with results.

to 1 year) and children older than age 1 year. There were no statistically significant differences in the IgG, IgM, and IgA distributions in relation to the normal values or mean concentrations of these immunoglobulins between the study and control group (p> 0.05). The results are shown in Table 3.

Also, the results of distribution of antibody concentrations in relation to the normal values in the groups of children separated according to the type of mother's immunosuppression (tacrolimus or cyclosporin regimen) were analyzed and compared between those groups and with the control group.

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There were no statistically significant differences in the IgG, IgM, and IgA concentrations according to the normal values and mean concentrations of these immunoglobulins between the group of children whose mothers used a particular immunosuppressive therapy regimen (based on tacrolimus or cyclosporin) and the control group ($p>0.05$).

There were no statistically significant differences in the IgG and IgM concentrations between the group of children whose mothers used the tacrolimus-based immunosuppressive regimen and the group of mothers receiving cyclosporine ($p>0.05$).

Comparing the IgA concentration distribution according to the normal values, a statistically significant difference was found in the IgA distribution according to the type of immunosuppressive regimens ($p<0.05$). We found that in the tacrolimus-based regimen, up to 70.7% of the subjects were normal and 29.3% were below normal. There were no results above the normal value. On the other hand, in the cyclosporin-based regimen group, the normal results were 54.5% and the results above normal value were observed in 27.3% of children. In this group, 18.2% of the results were below the normal value.

The comparison of mean IgG values in the analyzed groups according to the immunosuppression regimen did not show a statistically significant difference ($p>0.05$).

The analysis of mean IgM concentrations between the analyzed groups separated according to the mother's immunosuppressive regimen showed a statistically significant difference ($p<0.05$). We found that the mean IgM concentration in the tacrolimus-based regimen group was significantly lower than in the group of children born to mothers treated with cyclosporine-based regimen (0.693±0.58 [g/l] *vs.* 0.818±0.70 [g/l]).

Analysis of mean IgA concentrations according to the immunosuppressive regimen in mothers showed a statistically significant difference (0.390±0.63 [g/l] *vs.* 0.909±0.83 [g/l]) $p<0.05$. A significantly higher mean IgA concentration was found in children of mothers treated with a cyclosporin-based regimen.

Discussion

In recent years, the number of pregnant women after organ transplantation has systematically increased as has the number of children exposed in fetal life to long-term effects of immunosuppressants [5,7]. Transplantation leads to the reappearance of reproductive functions within a few months after surgery [1]. Proper functions of transplanted organ and well-monitored pregnancy allow alive delivery in about 75% of recipients [9]. However, such pregnancies are associated with increased risk of serious complications of both the mother and the fetus [10–12]. An increased risk of intrauterine growth restriction, low birth weight, miscarriage, stillbirth, and preterm birth, without a significant increase in congenital abnormalities are found. These complications result from maternal disease and immunosuppressive therapy [1,6,12–14]. The risk of infection, organ rejection, hypertension, and cesarean section is also elevated [11].

An important factor is the period of time between transplant surgery and pregnancy. Too short a period of time after surgery is associated with an increased risk of pregnancy loss, worsening of mother's health, and transplant rejection [1]. In the early post-transplant period, high doses of immunosuppressive drugs are used, which may affect the developing fetus. There is also a greater risk of infections associated with surgery and intensive care, as well as opportunistic and viral infections associated with high doses of immunosuppressive drugs [3].

Immunosuppressive therapy and the main disease which led to the liver failure and necessity of organ transplantation can affect the developing fetal organs, including the immune system, which is responsible for protecting the body against disease. Basic immune tests include serum IgG, IgM, and IgA levels [8].

Analysis of concentrations of these immunoglobulins in the group of children born to mothers who received immunosuppressive drugs during pregnancy compared with the control group (children of mothers who did not use this treatment) did not show statistically significant differences in mean concentrations and frequency distribution of defined outcomes according to the normal value (above normal, normal, below normal). This means that immunosuppressive therapy received by the mother does not significantly affect these parameters.

In the literature, there are few reports on the immune system of children born to women during immunosuppressive treatment due to connective tissue disease, inflammatory bowel disease, or organ transplantation, and the existing data are ambiguous. Various indications for the use of immunosuppressive drugs and the various doses of these drugs may have a significant impact on the results of the study and cause discrepancies [15,16]. In the case of autoimmune disease, immunosuppressive treatment usually involves 1 drug at a small dose, while treatment after organ transplantation is usually a high-dose multidrug or single therapy [17,18]. Motta et al. noted that in the case of autoimmune diseases, there is no significant effect of maternal treatment on the immune system of children, whereas in children born to mothers after organ transplants, the results are different and may be related to the dose and combination therapy used [18]. In other studies, on immunoglobulin concentration, similar to our present results, the findings did not demonstrate any correlation and

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no significant differences were found between the study group and control group.

In 2002, Schena et al. published a study of the immune system of 11 children of post-transplant mothers who received cyclosporine and methylprednisolone. At birth, they had normal IgG level and IgM and IgA levels below normal values, and after 2 months they had decreased IgG, IgM, and IgA levels. Immunoglobulin levels normalized by around 4 months of age, but IgG1 and IgG3 levels remained lower compared to the control group at up to 6 months of age. Despite the absence of clinical signs of immune dysfunction, the authors suggested postponement of vaccination in these children up to 6 months of age [19].

Our own study, published in 2014, included the analysis of IgG and Ig M concentrations in 39 children born to mothers after kidney transplantation who used immunosuppressive therapy and 39 children born to mothers who did not use immunosuppressants (control group). It did not show statistically significant differences between the groups [20].

Also, Ciamaz et al. compared IgG, IgM, and IgA levels in children born to mothers who took immunosuppressive drugs due to mesenchymal disease, and they did not show statistically significant differences between the study group and control group [16].

In a study published in 2007, Biggioggerro evaluated selected parameters of the immune system of children born to mothers who were treated with immunosuppressive drugs during pregnancy due to autoimmune diseases. The author did not find statistically significant differences in IgG, IgM, and IgA levels compared to the control group [21].

Motta et al. also compared IgG, IgM, and IgA levels *in vitro* between 19 children of mothers receiving immunosuppressive treatment for autoimmune diseases and the control group of 15 children whose mothers received only small doses of aspirin. There were no statistically significant differences between the 2 groups [15,18,22].

In 2005, Meregalli et al. presented an evaluation of the immune system of 9 children born to 6 mothers who received immunosuppressive medication (cyclosporin or dexamethasone) during pregnancy and 14 children in the control group whose mothers were diagnosed with an autoimmune disease and did not take immunosuppressants. There were no statistically significant differences in IgG concentrations, and all children had a normal response to type B vaccination [23].

Ersay et al. published a paper reviewing the immune system of a child born to a mother after kidney transplantation who received cyclosporine, azathioprine, and prednisolone. There was no increased incidence of infection. Postnatal immunoglobulin concentrations were normal, but in consecutive studies at 3 and 6 months of age, decreased IgG and IgA concentrations were observed, with normal IgM concentrations [24].

In 1993, Baarsma and Kamps published a study evaluating selected immune system parameters in the first 2 years of a child born to a mother after liver transplantation who received cyclosporine during pregnancy. No abnormalities of IgG, IgM, and IgA at birth and after 4 and 24 months were observed [25].

According to data from the literature, the concentrations of calcineurin inhibitors in umbilical cord blood are half the concentration in the mother's blood. Tacrolimus has the ability to accumulate in the placenta, where its concentration exceeds 3 times its concentration in the mother's blood, but in the fetal circulation it reaches half the rate of the mother [10].

Tacrolimus binds to specific cytoplasmic immunophilin (FKBP12) and inhibits calcium-dependent T cell signals cascade, thus preventing the transcription and synthesis of interleukins and other cytokines, and also inhibits the release of mediators of mast cells, basophils, and eosinophils.

Tacrolimus was administered to 41 (78.9%) mothers of the children in the study group. There were not reported any statistically significant differences in the distribution of IgG, IgM, and IgA concentrations compared to the normal values, and mean concentrations of these immunoglobulins between the study and control group of children whose mothers received a regimen based on tacrolimus. The analysis shows that the use of tacrolimus-based immunosuppressive regimens does not affect these parameters of the children's immune system.

Cyclosporin passes through the placenta and in the fetal plasma, according to some authors, reaches a level that is more than half the mother's plasma concentration [16,21]. Other reports show that only a small amount of cyclosporin passes into the fetal circulation [10]. Cyclosporin suppresses cellular and humoral immune responses and modifies inflammatory responses. It also affects the activation of TH lymphocytes, thereby indirectly inhibiting antibody production and macrophage activation. Cyclosporin effects occur in early phases of the cell cycle (G0 and G1). It reduces the formation and secretion of lymphokines.

It was reported that children with prenatal exposure to cyclosporine in the first year of life may have decreased maturation of T cells, B cells, and NK cells [19,26,27]. In several studies by different authors, in children born to mothers treated with cyclosporin, immune functions and response to vaccination were satisfactory [16,21–23,25,28].

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DiPaolo investigated the concentration of immunoglobulins G, M, and A in children of mothers after kidney transplantation taking cyclosporine during pregnancy. He showed that serum IgG concentration was normal during labor and IgA and IgM concentrations were low. At 2 months of age, total IgG level, with IgG1 and IgG3 and IgM and IgA subclasses were decreased. Immunoglobulin IgG, IgM, and IgA levels normalized at 4 months of age, but IgG1 and IgG3 subclasses were lowered until 6 months of age. The author did not find clinical signs of immunodeficiency in the study group, but due to reduced total T lymphocytes, CD4 + and CD8 + lymphocytes as well as B lymphocytes at 1 year of age, he suggested delayed vaccination. However, the study included only 6 children, without a control group [28].

In 2001, Tendrom collected results of several studies describing the effect of immunosuppressive therapy in pregnancy on children. The author, who based inter alia on the work cited above, suggests the postponement of vaccination in these children [5].

In the group of children born to mothers after transplantation, the prenatal exposure to cyclosporin involved 11 (21.1%) children. There were no statistically significant differences in the distribution of IgG, IgM, and IgA levels compared to the normal values and mean concentrations of these immunoglobulins between the group of children born to mothers treated with cyclosporin and the control group.

In our material, significant differences in distribution of IgA levels compared to the normal values in children, depending on the mother's immunosuppressive regimen (comparison of tacrolimus-based regimen, cyclosporin-based regimen) were found. There were no statistically significant differences in the distribution of IgG and IgM concentrations compared to the normal values between these groups of children.

Significant differences in mean concentrations of IgM and IgA were observed, depending on the mother's immunosuppressive regimen. Thus, the mean IgM concentration in the group of children born to mothers treated with tacrolimus-based regimen was significantly lower than that in children of mothers treated with cyclosporine-based regimen. In the case of a tacrolimus-based regimen, mean IgA levels were significantly lower than in the cyclosporin-based regimen. There were no statistically significant differences in mean IgG concentrations between the specified regimens.

In conclusion, the administration of tacrolimus-based regimen during pregnancy results in significantly lower mean IgA levels in the children, more frequent IgA values below normal and statistically significant lower mean serum IgM concentration compared to children whose mothers were treated with cyclosporine-based regimens. The study did not take into consideration the doses of the medications and possible effects of other medications in the treatment regimen. It is difficult to draw definitive conclusions, and further studies are needed to evaluate the possible effects of the type of immunosuppressive treatment on these parameters.

Limitations

Factors that may have had a significant effect on the results in the studied material and limit the value of the study are:

1. Heterogeneity of children of mothers after organ transplantation due to:
   a) various etiologies of diseases that lead to organ failure and various possible consequences.
   b) various treatment regimens and doses of medicines taken by mothers.
   c) different lengths of time between transplantation and conception.
   d) different functions of the transplanted organ.
2. Possibility of other diseases of the mother or child that may have a potential impact on the immune system.
3. Significant differences in the accuracy of measurements between laboratory in which IgG, IgM, and IgA levels were determined and the accuracy of reference values. For this reason, in addition to the comparison of the distribution of results according to the normal values between the study and control group, the mean concentrations of particular immunoglobulins were also compared.

Conclusions

1. Immunosuppressants administered to pregnant women after liver transplantation do not significantly affect the parameters of the immune system of their children in any of the age groups.
2. The type of immunosuppressive treatment in pregnant women may affect selected parameters of the immune system of children (e.g., mean IgA level, IgA level deviations compared to the norm value, and mean IgM concentration).
3. More long-term studies are needed with larger groups of patients to demonstrate possible long-term effects of fetal exposure to immunosuppressive drugs and a possible impact of the type of treatment on the children's immune system.

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