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Pregnancy management in prognosis for pregnant patients with systemic lupus erythematosus.

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Abstract

Objective: To study the effects of pregnancy management in prognosis for pregnant patients with systemic lupus erythematosus (SLE).

Methods: 217 pregnant patients who were diagnosed with SLE were divided into two groups, the control group and the intervention group. The intervention group was treated with routine treatment and nursing with additional pregnancy management, while the control group was treated with only routine treatment and nursing. Additionally, 195 normal pregnant women in the same period were selected as the healthy control. Regular laboratory tests were conducted for all subjects. Statistical analysis on changes of related disease indexes in each group was also performed. All information of maternal and neonatal outcomes was collected to record SLE activity rate, incidence of pregnancy induced hypertension (PIH), premature and fetal loss, neonatal weight and incidence of neonatal complications.

Results: Increased ANA titer and dsDNA, lower immunoglobulin complement, renal damage, blood system damage, increased SLEDAI score and BILAG score were observed in the control group and the invention group compared with the healthy control. Both the control group and the intervention group showed significant increase in the incidences of PIH, premature delivery, fetal loss and neonatal complications as well as significant decrease in neonatal weight compared with the healthy control. SLE activity rate and incidences of PIH, premature delivery and neonatal complications were significantly decreased while neonatal weight was greatly increased in the intervention group compared with the control group. Results of logistic analysis showed that low immunoglobulin complement, renal damage, increased dsDNA, increased dsDNA and low immunoglobulin complement were independent risk factors for increased SLE activity rate, fetal loss, premature delivery and neonatal complications, respectively.

Conclusion: The present study indicates that pregnancy management for pregnant SLE patients can significantly improve maternal and neonatal outcomes.

Keywords: Systemic lupus erythematosus, Pregnancy management, Maternal and neonatal outcome, Autoantibody to nuclear antigen, Low immunoglobulin complement.

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Introduction

Systemic lupus erythematosus (SLE) is a serious multi-system disease affecting various organs, predominantly in women of childbearing age (female: male ratio approximately 9:1) [1,2]. Generally, SLE is believed to have a correlation with heredity, and the environmental factors particularly include ultraviolet light exposure and oestrogen level [3]. The high oestrogen level is a major cause of SLE activity, since the rising oestrogen level enhances the prolactin level which results in increasing immune response even disorder, and at the same time, pregnancy will aggravate the burden on damaged heart and kidney so as to induce SLE activity [4]. Pregnancy with SLE is considered as a kind of high risk pregnancy, because SLE activity will be increased during pregnancy which causes vital organs damage and subsequently affects foetus of patients [5]. Moreover, the recurrence rate of SLE during pregnancy reached 13% to 68%, which may lead to spontaneous abortion, premature birth, stillbirth, intrauterine growth retardation, premature rupture of membrane and neonatal lupus erythematosus [1].

Currently, the treatment of SLE is mainly based on cortical hormone, and the unceasing enhancement of medical technology level helps the continuous progress in drug therapy and stem cell transplantation, so more and more SLE patients

have reproduction requirements [6]. Besides, one study has shown that the key for the reproduction of SLE patients is the timing of conception [7]. However, routine treatment alone cannot completely meet the reproduction requirements of patients [6], and it is important to explore the pregnancy management in pregnant SLE patients for maternal and child prognosis. So, the fertility level of SLE patients could be improved *via* the timing of conception, corresponding routine treatment and pregnancy management [8]. This study aims to explore the effects of pregnancy management on the maternal and neonatal prognosis of pregnant SLE patients.

Materials and Methods

Ethics statement

This study was performed with the approval of clinical management committee in our hospital. All patients in this study had signed the informed consents. All procedure was strictly conducted in accordance with the Declaration of Helsinki involving human beings.

Study subjects

A total of 217 pregnant SLE patients (all selective pregnancy) who admitted and diagnosed at the Department of Rheumatology in our hospital from January 2010 to November 2015 were recruited and divided into two groups, that is, the control group (n=96) and intervention group (n=121), in which the control group only received routine treatment and nursing while intervention group had additional pregnancy management. Meanwhile, a total of 195 pregnant women in the same period were included as normal group. All cases in the control group and the intervention group were in accordance with the diagnostic criteria of SLE recommended by American College of Rheumatology (ACR) in 1997 [9]. Except for tumour and connective tissue diseases, patients with four or more manifestations were diagnosed as SLE, including discoid erythema, cheekbone erythema, oral ulcer, photaesthesia, serositis, non-erosive arthritis, haematological abnormality, neural abnormality, immunological abnormality, renal lesion and positive antinuclear antibody. The systemic lupus erythematosus disease activity index (SLEDAI) was performed to classify clinical condition [10], that is, less than or equal to 4 points was regarded as non-active group, and greater than or equal to 5 points was regarded as active group. On the basis of lesion type, all patients were divided into skin lesion type, nephritis type, arthrosis type and non-positive immune antibody type. All SLE patients were voluntarily participated in this study, and the patients with other autoimmune diseases, infection and organ function failure were excluded.

Routine treatment and nursing method: prevention of cold and expectant treatment when having a fever; a good rest during SLE activity; avoiding of sunlight and high-light exposure; forbiddance of photosensitive drugs and food, and a diet of high protein, high vitamin, low sugar, low salt and low fat; calcium supplement and forbiddance of smoking, drinking and spicy food; observation of side effects upon using hormone and immunosuppressive agents.

Pregnancy management: during pregnancy, patients were monitored by the Department Gynaecology and Obstetrics and the Department of Rheumatology *via* regular electrocardiogram, ultrasound and ultrasound echocardiography and routine obstetric fetal monitoring, including determining gestational age in early pregnancy, detecting fetal development by ultrasound in middle pregnancy to determine fetal malformation preliminarily, and the late detection of fetal movement and fetal heart so as to determine periodic detection time and therapy, namely, prednisone 5-10 g/day to maintain stable condition, and hydroxychloroquine sulfate 0.1-0.2 g/day was added to original therapy if necessary (adjust dose and therapy according to the disease condition). Before delivery, the intramuscular injection of dexamethasone 10 mg/day was added for three days in order to promote the maturity of fetal lung. Three days after delivery, patients recovered to the original dose. Once patients had SLE activity or complications during detecting serological activity index, they need shock treatment with large doses of hormones even adding immunosuppressive agents, and if necessary, they also need blood transfusion, platelet transfusion and protein supplement. The indications for pregnancy termination should be considered on the basis of maternal and fetal conditions. When mother has severe complications, the pregnancy should be terminated right now no matter how long the pregnancy was. As for patients who were found placentas aging with mature foetus, once they had fetal distress or obstetrical indication, the pregnancy should be terminated *via* caesarean section or vaginal delivery.

Detection of disease index

The laboratory conducted regular detections for all patients in each group, including autoantibody to nuclear antigen (ANA), double stranded-DNA (dsDNA) antibody, immunoglobulin complement C_3, liver and kidney functions, blood routine examination, routine urine test and 24 h urinary protein quantity, in order to statistically analyse the changes of related indexes in each group. SLEDAI and British Isles Lupus Assessment Group (BILAG) were performed to score SLE patients [11].

Maternal and neonatal outcomes

During the research, all clinical features and the maternal and foetus outcomes were collected. Besides, SLE activity rate, incidence of pregnancy induced hypertension (PIH), incidence of premature delivery, incidence of fetal loss, and neonatal birth weight were observed and recorded. Moreover, whether new-borns had fetal growth restriction (FGR), neonatal lupus syndrome (NLS) and neonatal asphyxia were also observed so as to conduct the incidence of neonatal complications.

Statistical analysis

The statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA) software. All measurement data were expressed as mean ± standard deviation (SD), and *t*-test was used to compare the mean difference of continuous variable between two groups.

Enumeration data were expressed as percentage or ratio, which were compared by X^2 test. $P<0.05$ was considered statistically significant.

Results

Clinical feature of subjects among three groups

The clinical features of all the subjects in three groups were recorded. In the normal group, the age was 28.6 ± 5.2 years old, the weight was 55.7 ± 8.5 kg, and the gravidity was 2.1 ± 1.2; in the control group, the age was 27.8 ± 4.5 years old, the weight was 56.6 ± 3.2 kg, and the gravidity was 2.0 ± 1.0; in the intervention group, the age was 29.0 ± 4.9 years old, the weight was 57.4 ± 3.5 kg, and the gravidity was 1.8 ± 1.5.

As shown in Table 1, the analysis results showed that there were no significant differences in age, weight and gravidity among three groups (all $P>0.05$). Moreover, the analysis of clinical features including lesion type and disease condition type demonstrated no significant difference between the control group and the intervention group (all $P>0.05$).

Comparisons of disease indexes in each group

As shown in Table 2, the comparison of disease indexes in each group revealed that there were no changes in related disease indexes in the normal group. While in the control group and the intervention group, the related disease indexes were changed, including increased ANA titer, increased dsDNA titer, low immunoglobulin complement, renal damage, and blood system damage, increased SLEDAI score and BILAG score. When compared with the control group, the rate of patients in the intervention group with changed disease indexes were significantly lower (all P<0.05).

Table 1. *Basic clinical information for all participants before treatment.*

	Intervention n=121	Control n=96	Healthy n=195
Age, year	29.0 ± 4.9	27.8 ± 4.5	28.6 ± 5.2
Weight, kg	57.4 ± 3.5	56.6 ± 3.2	55.7 ± 8.5
Gravidity, month	1.8 ± 1.5	2.0 ± 1.0	2.1 ± 1.2
SLEDAI			
≤ 4	73 (60.3)	61 (63.5)	
≥ 5	48 (39.7)	35 (36.5)	
Lesion type			
Skin lesion type	48 (39.7)	37 (38.5)	
Nephritis type	34 (28.1)	28 (28.2)	
Arthrosis type	29 (24.0)	24 (25)	
Non-positive immune antibody type	10 (8.3)	7 (7.3)	

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index before treatment

Table 2. *Comparisons of disease indexes in each group.*

	ANA positive, n (%)	dsDNA positive, n (%)	Immunoglobulin complement C3, g/L	24h Proteinuria, positive, n (%)	Thrombocytopenia, n (%)	SLEDAI	BILAG
Healthy, n=195	13 (6.7)	2 (1.0)	1.39 ± 0.41	0 (0)	0 (0)		
Intervention, n=121	91 (75.2)	83 (68.6)	1.01 ± 0.36	81 (66.9)	17 (14.0)	4.2 ± 1.1	4.6 ± 1.2
Control, n=96	93 (96.9)	81 (84.4)	0.75 ± 0.24	79 (82.3)	25 (26.0)	5.1 ± 1.3	5.9 ± 1.6

Comparisons of maternal and neonatal outcomes

During the research, the analysis results about clinical features and the maternal and neonatal outcomes showed that, when compared with the normal group, patients in the control group and the intervention group had an obvious increase in the incidences of PIH, premature delivery, fetal loss and neonatal complications, and an evident decrease in neonatal weight (all $P<0.05$). Compared with the control group, patients in the intervention group had an evident decrease in SLE activity rate and incidences of PIH, premature delivery and neonatal complications (all $P<0.05$), but a great increase in neonatal weight ($P<0.05$). There was no significant difference in fetal loss between two groups ($P>0.05$) (Table 3).

Analysis of disease indexes related to the adverse maternal and neonatal outcomes

The data in the control group and the intervention group were combined to analyse the disease indexes that affecting the adverse maternal and neonatal outcomes. The univariate analysis revealed that the adverse maternal and neonatal outcomes were correlated with the increased ANA titer and dsDNA titer, low immunoglobulin complement, renal damage, and blood system damage as well as increased SLEDAI score and BILAG score (all P<0.05). With the adverse maternal and neonatal outcomes as dependent variable and with the disease indexes showing significant differences by univariate analysis as independent variables to conduct the logistic analysis. The

results showed that low immunoglobulin complement, renal damage, increased dsDNA titer, increased dsDNA titer were independent risk factors for adverse maternal and neonatal outcomes (all P<0.05) (Table 4).

Table 3. *Comparisons of disease indexes in each group.*

	Intervention n=121	Control n=96	Healthy n=195
PIH, n (%)	15 (12.4)	23 (24.0)	8 (4.1)
Premature delivery, n (%)	25 (20.7)	34 (35.4)	15 (7.7)
Fetal loss, n (%)	22 (18.2)	21 (24.0)	1 (0.5)
Complications of live birth			
Fetal distress, n (%)	13 (13.1)	19 (25.3)	3 (1.5)
Neonatal asphyxia, n (%)	5 (5.1)	10 (13.3)	2 (1.0)
Neonatal weight, kg	2.5 ± 1.1	2.1 ± 1.2	3.2 ± 1.4
SLE activity rate, n (%)	44 (36.4)	56 (58.3)	

Table 4. *Risk factors associated with adverse maternal and neonatal outcomes by Logistic multivariate regression analysis.*

	Wald	Odds ratio	95% CI	*P* value
ANA titer	3.125	1.234	(0.259~2.386)	0.016
dsDNA titer	2.456	1.056	(0.312~2.469)	0.023
Immunoglobulin complement C_3	2.689	2.335	(1.735~6.427)	0.008
Renal damage	5.247	3.126	(2.134~6.213)	0.005
Blood system damage	3.165	1.036	(0.572~2.823)	0.005
SLEDAI	7.613	5.164	(1.687~8.125)	0.031
BILAG	6.524	3.134	(1.257~6.439)	0.001

Discussion

SLE is a common chronic autoimmune disease affecting multiple organs with complicated clinical manifestations, which is once an important pregnancy contraindication [12,13]. Moreover, when combined with normal pregnant women, the pregnant SLE patients have a significant increase in obstetric complications such as spontaneous abortion, FGR, preeclampsia and intrauterine fetal death [14], which even causes nephropathy and PIH [15]. This study aims to explore the effects of pregnancy management on maternal and neonatal prognosis in pregnant SLE patients.

The results showed after routine treatment, pregnant SLE patients had a decrease in ANA titer and dsDNA titer, an increase in low immunoglobulin complement, a reduction in kidney and blood system damage and a decrease in SLEDAI score and BILAG score. Meanwhile, the proportion of deteriorated disease condition in patients who had pregnancy management was significantly decreased. During pregnancy, the immune response for women is mainly based on Th2 dominant immune response since Th1/Th2 response imbalance occurs, which results in high reactivity of B cells [16,17]. Here, B cells mediates the internal immune response, so the excessive activity of B cells, namely high reactivity of B cells, is a kind of abnormal immune response [18]. Furthermore, the high reaction of B cells in patients leads to abnormal immunological indexes involving complement level, ANA titer, dsDNA titer and low immunoglobulin complement [19]. During pregnancy management, prednisone was used to prevent the immune response caused by cellular immunity and to control SLE activity, which can prevent further deterioration of SLE [20], and later the proper monitor and treatment can effectively reduce the relevant conditions. Correspondingly, the levels of several risk factors, like internal complement and dsDNA antibody could be reduced *via* intervention treatments such as timing of conception and drug therapy so as to reduce the incidence of PIH [21].

Moreover, this study reported that after pregnancy management, pregnant SLE patients had a significant decrease in the incidence of SLE activity rate, PIH, premature delivery and neonatal complication and an evident increase in neonatal weight. The placenta sedimentation of immune complex and complement in serum in pregnant SLE patients leads to the damage of vascular endothelial cells and subsequently causes local microthrombus, thickened vessel wall and lumimal stenosis, which results in placental villi dysplasia, so their exchange function was affected, that is the nutrition supply to foetus was reduced, which finally gives rise to the higher incidences of recurrent spontaneous abortion, FGR, premature delivery, stillbirth and perinatal anoxia and ischemia [22]. Besides, a previous study also reported that the effective pregnancy management can reduce the incidences of fetal loss and premature delivery [23].

In addition, this study proved that low immunoglobulin complement, renal damage and dsDNA titer and low immunoglobulin complement were independent risk factors for increased SLE activity rate, fetal loss and neonatal complications, respectively. SLE patients' pregnancies mainly bring damages to kidney and blood system, which accelerates the deterioration of renal function, while the damages to skin and skeletal muscle are relatively mild [24,25]. Furthermore, spasm of uterus and relevant vessels caused by renal lesions leads to blood circulation disorder that blocks maternal and fetal blood exchange, resulting in fetal hypoxia even death, and especially the lupus nephritis will enlarge the risk of fetal loss [7].

To sum up, our study provides evidence that pregnancy management for pregnant SLE patients can significantly improve maternal and fetal outcomes. However, this study neither further explored the mechanism of pregnancy management for pregnant SLE patients, nor optimized the pregnancy management. Therefore, with limitation in results, it

is necessary to further explore the treatment and optimization of pregnancy management for pregnant SLE patients.

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