



The Fetomaternal Outcome of Autoimmune Diseases in Pregnancy

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Abstract

The immune system has got a remarkable ability to protect self from non self. An abnormality in this behavior results in a state called autoimmunity and the resultant diseases are called autoimmune diseases. Around 70% of the patients with autoimmune diseases are females. The common autoimmune diseases encountered in clinical practice are: Systemic Lupus Erythematosus, Immune Thrombocytopenic purpura, Type 1 Diabetes Mellitus, Myasthenia Gravis, etc. It is also seen that adverse pregnancy outcomes like abortions, spontaneous intrauterine deaths, abruptio, preterm labour, IUGR, gestational hypertension etc. are more common in this group of patients. Many of these diseases can result in good obstetric outcome in presence of a multidisciplinary approach and good antenatal care. In this study the fetal and maternal complications encountered in patients with autoimmune diseases are studied. This, being a descriptive study, a complete understanding of the disease process may not be obtained. According to the yearly statistics in our hospital, in the last five years, there have been around 15- 20 cases of SLE, APLA and ITP, fewer cases of Type Diabetes Mellitus and Myasthenia Gravis. My study would be to summarize the fetal and maternal outcomes in these diseases and to draw possible conclusions. The diseases taken for study are Systemic Lupus Erythematosus, Primary Antiphospholipid Antibody Syndrome, Immune Thrombocytopenic Purpura and Type 1 Diabetes Mellitus.

Objectives

Primary Objective

- To study the fetomaternal outcome of autoimmune diseases in pregnancy in a tertiary care centre. 1

Secondary Objective

- To find out the association of autoimmune diseases with various adverse pregnancy outcomes in the study group.
- To identify the various fetal complications of autoimmune diseases in the study group

Materials and Methods: This was a descriptive study conducted in Department of obstetrics and gynaecology, Sree Avittom Thirunal Hospital (SATH), Medical Colleg, Thiruvananthapuram from January 2012 to November 2012 Study Population included patients with already diagnosed cases of Autoimmune Diseases registered in Sree Avittom Thirunal Hospital, Thiruvananthapuram which is a tertiary care centre, are taken for the study.

Conclusion: *In the present study, 44.4% of the patient had SLE , 25% of the patients had APLA and 19.4% had ITP. In the present study about most of them were multigravidas. Among these multigravidas, about 71.4% had previous history of abortions and 42.8% had previous history of more than 2 abortions. Among the 16 patients of SLE 4 patients (25%) had previous history of two or more abortions. Out of the 36 patients in the study, only 12 patients (33.4%) had history of previous pregnancy reaching period of viability. Out of these 33.33% were SLE patients. Out of the 28 multigravidas under study only 5 patients (17.8%) had a previous successful birth outcome. It was observed that 41.7% had to be treated with steroid alone, 27.8% needed heparin and 11.1 % needed both. In SLE patients, 62.5% were on steroid alone and 25% of them were on both steroid and heparin. Out of those taking both steroid and heparin, 1 had secondary APLA. The group of drugs most commonly given to pregnant women with SLE is the glucocorticoid preparations, both as maintenance therapy. Among the patients who were given heparin alone, 80% were patients of primary APLA. Of the 36 patients studied, 11.1% of the patients developed thrombosis. Of them all were patients of SLE, of which one case of maternal death due to intracranial thrombosis was reported. This reflects the devastating effect of the disease and also the maternal mortality due to vascular thrombosis. Among the two cases of intrauterine death, one had primary APLA for 2 years duration and the other had uncontrolled diabetes. Hence diabetes should be strictly controlled during pregnancy. Out of the 36 patients, 27.8% had preterm deliveries and 16.7% had abortions. Out of abortions, 3 (50%) patients had SLE and 3 (50%) had APLA. Among the abortions 66.7% were second trimester abortions and 50% of them had SLE. This shows that abortion after appearance of cardiac activity occurred more with APLA and preterm births occurred more with SLE. Around 56.7% of the patients needed caesarean sections , the patients being the high risk group the incidence of operative delivery is more in them. 53.3% of the babies had low birth weight and 50% of their mothers had SLE, showing that the incidence of intrauterine growth restriction and small for gestational babies is more in patients with autoimmune diseases. The important take home message is that autoimmune diseases are very commonly associated with complications like preterm deliveries, abortions, GHTN, intrauterine deaths. Hence they require good counseling and antenatal care an multidisciplinary approach in a tertiary centre.*

Introduction

The immune system has got a remarkable ability to protect self from non self. An abnormality in this behavior results in a state called autoimmunity and the resultant diseases are called autoimmune diseases.¹ Around 70% of the patients with autoimmune diseases are females.

The common autoimmune diseases encountered in clinical practice are: Systemic Lupus Erythematosus, Immune Thrombocytopenic purpura, Type 1 Diabetes Mellitus, Myasthenia Gravis, etc. It is also seen that adverse pregnancy outcomes like abortions, spontaneous intrauterine deaths, abruption, preterm labour, IUGR, gestational hypertension etc. are more common in this group of patients¹the magnitude of the problem is largely unknown in developing countries. Appropriate treatment and early identification of complications can reduce the mortality and morbidity to a great extent.

Rationale of the study

The prevalence of autoimmune diseases in general population is low. It is very well recognized now that a myriad of clinical manifestations can occur in autoimmune diseases. Obstetric manifestations including recurrent miscarriages, early onset of pre eclampsia, intrauterine growth restriction, abruption occur in these diseases. These patients are at increased risk of recurrence of complications in subsequent pregnancies. The risk of recurrent pregnancy losses and thrombotic complications is very high in diseases like SLE and APLA. Complications like congenital anomalies, miscarriages, intrauterine deaths etc. are very commonly associated with Type 1 Diabetes Mellitus. Many of these diseases can result in good obstetric outcome in presence of a multidisciplinary approach and good antenatal care.

There are only very few studies conducted on these diseases. Sree Avittom Thirunal Hospital being a referral centre caters women with these

diseases also. In this study the fetal and maternal complications encountered in patients with autoimmune diseases are studied. This, being a descriptive study, a complete understanding of the disease process may not be obtained.

According to the yearly statistics in SAT, in the last five years, there have been around 15- 20 cases of SLE, APLA and ITP, fewer cases of Type Diabetes Mellitus and Myasthenia Gravis. My study would be to summarize the fetal and maternal outcomes in these diseases and to draw possible conclusions.

The diseases taken for study are Systemic Lupus Erythematosus, Primary Antiphospholipid Antibody Syndrome, Immune Thrombocytopenic Purpura and Type 1 Diabetes Mellitus.

Objectives

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- To find out the association of autoimmune diseases with various adverse pregnancy outcomes in the study group.
- To identify the various fetal complications of autoimmune diseases in the study group

Materials and Methods

Design of the study: Descriptive study

Setting: Department of obstetrics and gynecology, Sree Avittom Thirunal Hospital (SATH), Medical College, Thiruvananthapuram

Duration of the study: January 2012 to November 2012

Study Population: Patients with already diagnosed cases of Autoimmune Diseases registered in Sree Avittom Thirunal Hospital, Thiruvananthapuram which is a tertiary care centre, are taken for the study. As the prevalence of the disease is very low, the gestational age at registration is not taken into consideration. Diseases are systemic lupus erythematosus,

Primary Anti phospholipid antibody syndrome, myasthenia gravis, autoimmune thrombocytopenic purpura, type I diabetes mellitus. These diseases were included after fulfilling standard inclusion criteria

Method of Study

These patients with the above autoimmune diseases are recruited in the study. They are followed up till delivery. The maternal complications like Gestational Hypertension, thrombosis, Gestational Diabetes mellitus, preeclampsia, postpartum haemorrhage are studied. The fetal complications studied are intrauterine growth restriction, intrauterine death, preterm birth, low birth weight are studied.

Sample Size and Plan of Analysis

As the prevalence of the diseases is very low, all cases attending and delivering in the institution during the study period are included. The data is analyzed using package Excel /SPSS.

Observations and Results

1. Disease distribution

Out of the 36 patients studied, 16 (44.4%) had SLE.

9 (25%) had Primary APLA.

1 (2.8%) had Myasthenia gravis.

7 (19.4%) had Autoimmune Thrombocytopenic Purpura.

3 (8.3%) had Type 1 Diabetes Mellitus.

2 Age Distribution: In the present study about 66.6% of the patients belonged to the age group below 28 years. The mean age of the study population was 22 years

3. Distribution based on education

Education	Frequency	Percent
Middle school	13	36.1
High school	17	47.2
Higher secondary	5	13.9
Degree	1	2.8
Total	36	100.0

36.1% of the population had only middle school education. 47.2% had high school education.

1. Distribution based on obstetric score

gravida	Frequency	Valid Percent	SLE	APLA	MG	ITP	DM
Primi	8	22.2	2	0	0	4	2
2 nd gravida	12	33.3	8	0	1	2	1
3 rd gravida	11	30.6	2	8	0	1	0
4 th gravida	2	5.6	2	0	0	0	0
5 th gravida	2	5.6	1	1	0	0	0
6 th gravida	1	2.8	1	0	0	0	0
Total	36	100.0	16	9	1	7	3

Of the 36 patients in the study, 77.8% were multigravidas.

2. Distribution based on history of abortions

Gravida	Abortions				Total	
	Present		Absent		N	%
	N	%	N	%		
>1	20	71.4%	8	28.6%	28	100.0

Out of these 77.8% multigravidas, about 71.4% had previous history of abortions.

3. Distribution based on number of abortions

Out of the 28 multigravidas in the study population 42.8% patients had previous history of 2 or more abortions.

4. Distribution based on parity

Out of the 36 patients in the study, only 12 patients (33.4%) had history of previous pregnancy reaching period of viability

5. Distribution based on previous successful birth outcome

Out of the 28 multigravidas under study only 5 patients (17.8%) had a previous successful birth outcome.

8. Distribution based upon the complication

"Complications	Frequency	SLE	APLA	MG	ITP	DM
Nil	8(22.2%)	1(2.78%)	3(8.33%)	1(2.78%)	2(5.56%)	1(2.78%)
ghtn	10(27.8%)	6(16.67%)	3(8.33%)	0	0	1(2.78%)
Preeclampsia	1(2.8%).	0	1(2.78%)	0	0	0
Diabetes	4(11.1%)	3(8.33%)	0	0	1(2.78%)	0
Thrombocytopenia	2(5.6%)	0	0	0	2(5.56%)	0
Others	6(16.7%)	4(11.11%)	0	0	1(2.78%)	1(2.78%)
ghtn+dm	5(13.9%)	2(5.56%)	2(5.56%)	0	1(2.78%)	0
Total	36	16	9	1	7	3

Out of the 36 patients studied, 27.8% developed GHTN, 13.9% developed both GHTN and GDM, 5.6% patients developed thrombocytopenia.

6. Distribution based on the treatment taken

It was observed that 41.7% were treated with steroid alone, 27.8% needed heparin and 11.1 % needed both

7. Distribution based on duration of the disease

It was seen that 75 % of the patients had the disease for less than 2 year

Patient of SLE died due to intracerebral thrombosis.

9. Distribution based on presence of thrombosis

Of the 36 patients studied, 11.1% of the patients developed thrombosis. Out of these, one case was a 23 year old lady G 5 A 4, a known case of SLE with a disease duration of 3 years.

10. Distribution of intra uterine death

There were 2 cases of intrauterine deaths in the study. One was the case of APLA and another was the case of type I diabetes mellitus

13. Distribution of neonatal outcome

Outcome	Frequency	Valid Percent	SLE	APLA	MG	ITP	DM
Term	20	55.6	7(19.44%)	4(11.11%)	1(2.78%)	7(19.44%)	1(2.78%)
Preterm	10	27.8	6(16.67%)	2(5.55%)	0	0	2(5.55%)
Abortion	6	16.7	3(8.33%)	3(8.33%)	0	0	0
Total	36	100.0	16	9	1	7	3

Out of the patients under study, 55.6% had term deliveries, 27.8% had preterm deliveries and 16.7% had abortions

14. Distribution based on the time of abortion

Out of the 6 abortions, 4 (66.7%) were second trimester abortions.

15. Distribution base on the time of preterm deliveries

Out of the 10 preterm deliveries, 80% were above 34 weeks of gestation.

16. Distribution of mode of delivery

Out of the 30 patients 56.7% of the patients underwent LSCS for obstetric indications.

17. Distribution according to birth weight

Out of the 30 babies 53.3% of the babies had a birth weight of < 2.5kg

18. Comparison of Gestational age and weight

Out of the above mentioned 53.3% babies, 37.5% of the babies were term babies.

19. Distribution based on the Apgar scores of babies

Out of the 28 live births around 85.7% had APGAR Scores of 8 or more than 8.

20. Distribution of Meconium stained liquor.

No cases of Meconium stained were reported.

11. Prevalence and Distribution of IUGR

Out of the 30 patients who crossed the age of period of viability, 8 patients (26.7%) developed IUGR. Thus the prevalence of IUGR was 26.67%

12. Distribution based on PPH

There were two cases of mild postpartum hemorrhage, one was a case of ITP and the other was a case of SLE.

21. Distribution of Anomalies.

No cases of anomalies were reported.

22. Distribution of Still birth.

No cases of still births were reported

23. Comparison between duration of disease and outcome.

A) SLE

In SLE, there were 3 cases of abortions. Two of them had a disease duration of 1 to 2 years and one had a disease duration of 2 to 5 years.

B) Primary APLA

Out of the 3 abortions in primary APLA 1 had a duration of >1 year. Out of the 2 preterm deliveries one had a duration of > 1 year

Discussion

Out of the patients studied 44.4% had SLE, 25% had Primary APLA, 19.4% had AITP, 2.85% had myasthenia Gravis, and 8.3% had Type 1 Diabetes Mellitus. This is in concordance with the yearly statistics in SAT where many SLE patients are referred.

In the study 66.6% of the patients belonged to the age group of below 28 years, with a mean age of 22 years. This keeps in line with the deliveries taking place in SATH, where the maximum number of deliveries occur in this age group

Among the patients studied, 69.4% belonged to rural areas which is in accordance with the population taking treatment from the institution.

30.6% of the population had a monthly income of Rs.2936-4893, which is in accordance with the population attending SAT hospital.

66.7% of the study population were Hindus, 19.5% were Christians and 47.2 % the patients had high school education.

In the present study 77.8% were multigravidas. Among these multigravidas, 71.4% had previous history of abortions and 42.8% had previous history of 2 or more than 2 abortions. Among the 16 patients of SLE 4 patients (25%) had previous history of two or more abortions. It was seen that 50% these patients had a disease duration of 2 or more than 2 years. Out of the SLE patients, 25% had a flare and 2(50%) of them ended up in miscarriages. In a study it was seen that fetal prognosis depends mostly on disease activity, with fetal loss ranging from 25-52% in patients with active SLE compared to 8-12% in patients with inactive SLE at the onset of pregnancy. The latter rate is comparable to observations in healthy women.^{1,2,3}

Out of the 7 patients with ITP only 1 patient had previous history of abortion and 1 had previous history of intrauterine death. In a study to evaluate perinatal outcome and medications used for pregnancies complicated by ITP perinatal outcome of pregnancies with ITP is generally found to be good. j

Out of the 36 patients in the study, only 12 patients (33.4%) had history of previous pregnancy reaching period of viability. Out of these 33.3% were SLE patients. Out of the 28 multigravidas under study, only 5 patients (17.8%) had a previous successful birth outcome. Out of them 2 were SLE patients, 2 were ITP patients and 1 was a patient with Myasthenia Gravis. One of these SLE patients had less than 2 year duration of the disease. In the study on pregnancy outcome in SLE sixty patients with 103 pregnancies were evaluated. There were 68 live

births, 15 spontaneous abortions, 12 stillbirths and eight therapeutic abortions.

It was observed that 41.7% were treated with steroid alone, 27.8 % needed heparin and 11.1 % needed both. Out of the 16 SLE patients, 62.5% were on steroid alone and 25% of them were on both steroid and heparin. Out of those taking both steroid and heparin, 1 had secondary APLA. The group of drugs most commonly given to pregnant women with SLE is the glucocorticoid preparations, both as initiation and maintenance therapy. Among the patients who were given heparin alone, 80% were patients of primary APLA. At present, maternally administered heparin is considered the treatment of choice in Primary APLA; it is usually initiated in the early first trimester after ultrasonographic demonstration of a live embryo. Treatment with heparin and aspirin is emerging as the therapy of choice, with ~75% of treated women with RPL and APLS having a successful delivery compared with <50% without treatment.

Most commonly reported complication was Gestational hypertension. Out of the 10 patients with GHTN alone, 60% had SLE and 40% had APLA. The median rate of gestational hypertension/preeclampsia in pregnancies complicated by APS is 32%, with a range up to 50%. It appears that between 20% and 30% of women with SLE develop either gestational hypertension or preeclampsia (gestational hypertension with proteinuria)'. Out the patients with both GDM and GHTN 40% were SLE patients. During pregnancy, chronic glucocorticoid therapy has also been associated with an increased risk of glucose intolerance.

Out of the 4 patients with secondary APLA, all were secondary to SLE. Mok *et al.* studied 91 pregnancies, reporting that antiphospholipid antibodies were more prevalent in patients with recurrent miscarriages and the strongest predictive factor was the presence of lupus anticoagulant.⁴ One-third of the patients have APS secondary to systemic lupus erythematosus (SLE). This high

percentage of the disease is due the selective population studied.

Of the 36 patients studied, 11.1% of the patients developed thrombosis. All of them were patients of SLE, of which one case of maternal death due to intracranial thrombosis was reported. She was a case of SLE for more than 3 years duration. On comparing the maternal mortality ratio of the institution it is found to be 3 times more. Out of these 50% cases had secondary APLA. Among the most prominent features associated with antiphospholipid syndrome (APS) are cerebral ischaemic events (CVE). Pregnancy with APS increases the risk of thrombosis, including CVE.⁵ The Near miss mortality cases were a) a case of eclampsia in a patient with Primary APLA b) A case of Diabetic cardiomyopathy c) A case of diabetic Nephropathy.

Out of the 36% patients, two developed intrauterine death. One of them was a case of APLA with a disease duration of 2 years and the other was a case of Type 1 DM. In a study conducted about pregnancy loss in Antiphospholipid syndrome, it is seen to be associated with recurrent miscarriage. Pregnancies that survive the first trimester risk developing pre-eclampsia, intrauterine growth retardation and fetal distress during labour. Pregnancy loss is initially caused by defective embryonic implantation and later by thrombosis of the placental vasculature. In women with antiphospholipid antibodies, thromboprophylaxis during pregnancy improves the live birth rate⁶.

In the study, 8 patients (26.7%) developed intrauterine growth restriction. 6 of them that is 75 % of these patients had SLE or APLA. Dhar *et al* reviewed 16 studies on pregnancy outcomes before and after the diagnosis of SLE.⁷ and found that, in spite of some limitations in study design and statistical analysis and variations in terminology used, most studies concluded that pregnancy loss preterm births and IUGR were more common after than before the diagnosis of SLE and compared to a control population. Relatively high rates of IUGR occur in association

with antiphospholipid antibodies. 'Even with currently used protocols the rate of IUGR approaches 30%.'

Out of the 30 patients, 2 cases developed Post partum haemorrhage. One was a case of ITP with low platelet count and required 4 platelet concentrates and another was a case of SLE.

Out of the 36 patients, 27.8% had preterm deliveries and 16.7% had abortions. Out of abortions, 3 (50%) patients had SLE and 3 (50%) had APLA. Among the abortions 66.7% were second trimester abortions and 50% of them had SLE (1 had secondary APLA) and 50% had APLA. In the study on pregnancy outcome in SLE sixty patients with 103 pregnancies were evaluated. There were 68 live births, 15 spontaneous abortions, 12 stillbirths and eight therapeutic abortions. Of liveborn infant births, 19 were premature, 24 had suffered intrauterine growth restriction and one had neonatal lupus.

Among the patients with preterm deliveries, 60% had SLE. Among them 80% were above 34 weeks of gestation. Dhar *et al* reviewed 16 studies on pregnancy outcomes before and after the diagnosis of SLE⁷ and found that, in spite of some limitations in study design and statistical analysis and variations in terminology used, most studies concluded that pregnancy loss preterm births and IUGR were more common after than before the diagnosis of SLE and compared to a control population. Preterm birth has been reported in as few as 3% and as many as 73% of pregnancies complicated by SLE.^{8,9}

In the study, 56.7% underwent LSCS for obstetric indications. There were not many studies regarding the mode of delivery in autoimmune diseases.

Among the patients 53.3% of the babies had a birth weight less than 2.5 kg. Out of them 50% had SLE. 37.5% of them were term babies. Uteroplacental insufficiency resulting in IUGR or small-for-gestational-age neonates occurs in between 12% and 40% of pregnancies with SLE.^{10,11}.

In the study it was observed that as the duration of the disease increased, the association with adverse pregnancy outcome increased. There is general agreement that SLE pregnancy outcomes are more likely to be complicated. In one prospective study, increased rates of hypertension during pregnancy, preterm delivery, unplanned cesarean delivery, postpartum hemorrhage, and maternal venous thromboembolism were all more frequent in women with SLE than others fetal growth restriction and neonatal deaths were also more often seen in association with SLE There were no congenital anomalies reported in the study.

Conclusion

Majority of the patients in the study had SLE 25% of the patients had APLA and 19.4% had ITP. Most of the patients belonged to the rural area, 77.8% were multigravidas. Among these multigravidas, about 71.4% had previous history of abortions and 42.8% had previous history of more than 2 abortions. Among the 16 patients of SLE 4 patients (25%) had previous history of two or more abortions. 12 patients (33.4%) had history of previous pregnancy reaching period of viability. Out of these 33.33% were SLE patients. It was observed that 41.7% had to be treated with steroid alone, 27.8% needed heparin and 11.1% needed both. Out of the 16 SLE patients, 62.5% were on steroid alone and 25% of them were on both steroid and heparin. The group of drugs most commonly given to pregnant women with SLE is the glucocorticoid preparations, both as maintenance therapy. Among the patients who were given heparin alone, 80% were patients of primary APLA. Of the 36 patients studied, 11.1% of the patients developed thrombosis. Of them all were patients of SLE, of which one case of maternal death due to intracranial thrombosis was reported. Among the two cases of intrauterine death, one had primary APLA. Out of the 36 patients, 27.8% had preterm deliveries and 16.7% had abortions. Out of abortions, 3 (50%) patients had SLE and 3 (50%) had APLA. Among the abortions 66.7% were second trimester abortions

and 50% of them had SLE. This shows that abortion after appearance of cardiac activity occurred more with APLA and preterm births occurred more with SLE. Around 56.7% of the patients needed caesarean sections, the patients being the high risk group the incidence of operative delivery is more in them. 53.3% of the babies had low birth weight and 50% of their mothers had SLE, showing that the incidence of intrauterine growth restriction and small for gestational babies is more in patients with autoimmune diseases. The important take home message is that autoimmune diseases are very commonly associated with complications like preterm deliveries, abortions, GHTN, intrauterine deaths. Hence they require good counseling and antenatal care an multidisciplinary approach in a tertiary centre.

Recommendations

- Large multicentric collaborative studies are needed to obtain larger patient population.
- Follow up of the women for a longer duration is to be instituted..
- A register should be maintained for these patients so that they can be identified easily in any clinical emergency when they come with different clinical scenario.
- The babies need to be followed for their long term neurological development and recurrence of the maternal disease in them.
- The feasibility for successful pregnancy outcome and the need for control of disease to be ensured by prenatal care and counseling clinics with a multidisciplinary team approach

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