INTRODUCTION

1. Urgency of topics

Recurrent pregnancy loss (RPL) are a common maternity pathology affects 1-3% pregnancy. RPL is defined as having 3 times more consecutive miscarriages, eliminating cases of ectopic pregnancy, hydartiform mole and fetal biochemical abortion should under 20 weeks. The most common causes and can be cured completely of RPL is antiphospholipid syndrome (APS), the antiphospholipid antibody (aPL) causes thrombose in the placenta vessels, which triggers RPL in the first 3 months, stillbirth, fetal growth retardation or premature, severe preeclampsia and so on. Diagnosis and treatment APS can raise the live birth rate from 20% up to 80%. Since 2009, Vietnam obstetricians has begun to learn and initially identified the role of APS in RPL. However, obstetric physicians realize that there are many obstacles in the application of criteria for diagnosing subclinical syndrome in patient populations of RPL. Several studies conducted in Vietnam has not yet fully examined the two main types of aPL, or not tested twice for patients with positive result to eliminate fault positive cases.

Therefore, the theme: "Research antiphospholipid syndrome in pregnant women with a history of RPL by 12 weeks" was conducted with two objectives:

(1) To analyse of obstetric history and characteristics of anticardiolipin antibody and lupus anticoagulant in pregnant women with a history of RPL.

(2) To assess the effectiveness of treatment pregnancy in women with a history of RPL by antiphospholipid syndrome by coordinating regimen low doses of aspirin and low molecular weight heparin.

2. New contributions of topics

(1) Research conducted on a large enough sample 301 pregnant women with a history of RPL and patients have been tested 2 main antibodies: aCL and LA. The study tested 2 times for the positive cases in order to eliminate all cases of transient positive. The study results showed that is the most common cause of RPL, accounted for 11, 29%.

(2) The study has identified the primary aPL in RPL is IgM aCL (8, 97%) and positive value of the aCL in RPL is at the average level, lower than with common standards applicable to general APS status.

(3) The treatment conducted in accordance with guidelines issued by the American Society for Reproductive Medecine, the rate the live birth rate achieved in the study was 91.18%. This was the first study of Vietnam which treated pregnant women until 34 weeks gestation and monitored patients until delivery. The treatment of combination aspirin and lovenox 20 mg / day to 91 patients has been safe and effective.

3. Layout thesis

The thesis includes 127 pages, 29 tables, 9 graphs, 6 pictures and 107 references. Background: 2 pages; Chapter 1 Overview: 35 pages; Chapter 2 Objects and Research Methodology 13 pages; Chapter 3 Results: 35 pages; Chapter 4 Comment: 39 pages; Part Conclusion: 2 pages; Recommendations: 1 page.

Chapter 1: LITERATURE REVIEW

1.1. Recurrent pregnancy loss

RPL is defined as having 3 times more consecutive miscarriages, eliminating cases of ectopic pregnancy, hydartiform mole and fetal biochemical abortion should under 20 weeks. The incidence of 2 consecutive miscarriages is 5%, 3 times in a row is 2%. There are 5 main reasons: gen-chromosomal abnormalities, uterine abnormalities, endocrine disorders, immune disorders and coagulopathy. In that APS is an autoimmune disease most commonly lead to RPL 5% - 20%.

1.2. Antiphospholipid syndrome

1.2.1. Definitions: Antiphospholipid syndrome (APS) was first defined as a syndrome in 1983,1 consisting of a triad of manifestations involving arterial and/or venous thrombosis, recurrent fetal loss, accompanied by mild to moderate thrombocytopenia and elevated titers of antiphospholipid (aPL) antibodies: lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL).

1.2.2. Diagnostic criteria: based on Sydney criteria 2006

* Clinical criteria:

(1) Vascular thrombosis: One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.

(2) Pregnancy morbidity (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, (b) One or more premature births of a morphologicallynormal neonate before the 34th week of gestation (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

* Laboratory criteria:

(1) LAC present in plasma, on 2 or more occasions at least 12 weeks apart.

(2) aCL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titers (i.e., greater than 40 GPL or MPL, or greater than the 99th percentile), on 2 or more occasions, at least 12 weeks apart.

(3) Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titers greater than the 99th percentile), present on 2 or more occasions, at least

12 weeks apart.

1.3. Treatment RPL acquired APS

Treatment consists of two methods:

(1) treatment reduced the production of antibodies with corticoide or intravenous immunoglobulin. This treatment method is not highly effective and have more side-effects, being abandoned so far.

(2) Treatment using anticoagulants such as aspirin and heparin to prevent embolism occurred in trophoblast vessels. Royal Colledge of Obstetrician and Gynecology recommends the treatment of low-dose aspirin coordination and heparin to increase the rate of fetal life. American Society for Reproductive Medecine recommends the treatment of low - dose of aspirin (81 mg daily) and heparin (10,000 units a day).

Chapter 2: SUBJECTS AND METHODS

2.1. Research subjects

2.1.1. Selection criteria

For objective 1:

(1) A history of two consecutive miscarriages, gestational age by 12 weeks.

(2) Patients with pregnancy (HCG test positive and ultrasound images showing an amniotic sac in the uterus).

(3) The patients were tested for antibodies LA and aCL.

For objective 2:

All patients meet the selection criteria in objective 1 and having test: IgM aCL positive and / or IgG of aCL positive and / or LA positive will be treated and monitored according to the protocol of the study research.

2.1.2. Exclusion criteria

For objective 1:

(1) Patients were positive for aPL in the first test but did not test for the second time after 12 weeks.

(2) Patients had late consecutive miscarriages after 12 weeks. (3) Patients had consecutive miscarriages but those pregnancies were molar pregnancy or ectopic pregnancy.

For objective 2:

(1) Includes the applicable exclusion criteria for objective 1.

(2) The patients who did not follow research's treatment.

(3) The case is contraindicated with lovenox.

2.1.3. Location and time study

The study was carried out in National Hospital of Obstetrics and Gynecology from 1/1/2012 to 1/7/2014.

2.2. Research Methods

2.2.1. Study design:

(1) The cross-sectional study to find the rate of APS among RPL and other causes. Prospective cohort study to analyze obstetric history of RPL patients and analyze the characteristics of antiphospholipid antibodies in patients with RPL.

(2) Nonrandomized trial to evaluate the effectiveness of combination of low-dose aspirin and low molecular weight heparin for RPL patients acquired APS.

2.2.2. Sample size for 2 objectives:

From the results of the two formulas on the sample size, the study will select larger sample size is 254 in order to meet the 2 study objectives outlined.

2.2.3. Conducting research for patients

Through asking patients, medical examination and laboratory research conducted following steps:

Step 1: Find the other cause of RPL.

Step 2: Find the aCL and LA. Negative results → Group RPL aPL negative.

Step 3: The 1st positive patients will be treated with low-dose aspirin and low molecular weight heparin.

Step 4: After 12 weeks from the first test, possitive will be test for

the second time: The negative patients: stop anticoagulation therapy. The continuing positive patients – APS patients will be treated until 34 weeks.

2.2.4. The treatment regimens applied for RPL patients acquired APS:

(1) Aspirin 100 mg/day.

(2) Low molecular weight heparin (lovenox) 20 mg/day, administered subcutaneously.

(3) Calcium tablet 500 mg/day.

The begining time as soon as ultrasound image shows the amniotic sac in the uterus.

Duration of treatment: Group 2 times positive until 34 weeks of gestation. Group 1 time positive will not treat as soon as negative test found out.

2.2.5 Treatment follow up:

Outpatient treatment at the Clinic department of National hospital of Obstetrics and Gyneoclogy: examination, ultrasound exam and blood tests. Blood tests including platelet counts, weekly in the first 4 weeks, then monthly until the end of treatment regimens.

2.2.6. Data processing: Data processing software: The data collected from the research program are entered into Excel, then is converted into data analysis software SAS version 8:02 (SAS Institute, Cary, NC, 2003). Using statistical algorithms to process the data.

2.3. **Research Ethics**: In Vietnam, patients with a history of RPL are not tested for aPL before having pregnancy. To ensure all patients at risk of APS will be treated early, any aPL positive patients will be

treated by aspirin and lovenox. After 12 weeks, patients will be tested again if the results were negative, patients will stop further treatment. But all the results of research on the APS will be calculated based on patients with a double positive results. This research project is an branch of the Ministry of Health's project, called: "Research the process of diagnosis and treatment protocols antiphospholipid syndrome in women with a history of RPL " in 2012, by Associate Prof. Cung, Thi Thu Thuy, MD., Ph.D.

Chapter 3: RESULTS OF THE STUDY

3.1. Percentage of APS in RPL patient

Table 3.1. Triage according antiphospholipid syndrome

<table>
<tr><th colspan="2">aPL antibodies</th><th>Number of patients</th><th colspan="2">Rate%</th></tr>
<tr><td rowspan="2">RPL non APS (n =267)</td><td>Negative</td><td>210</td><td>69.7</td><td rowspan="2">88.1</td></tr>
<tr><td>Positive 1 times</td><td>57</td><td>18.4</td></tr>
<tr><td>RPL acquired APS (n=34)</td><td>Positive 2 times</td><td>34</td><td colspan="2">11.29</td></tr>
<tr><td colspan="2">Total</td><td>301</td><td colspan="2">100.00</td></tr>
</table>

301 RPL patients eligible to participate in research, the incidence of APS accounted for 11.29%.

3.2. History characteristics of RPL patients

Comparison between two groups of RPL non APS and RPL acquired APS shows that number of miscarriages, abortion time and number of children living are similar in two groups. Only a history of medical problems related to APS such as premature birth, early severe preeclampsia, stillbirth and fetal growth retardation in APS group was 14.7% higher than that of non APS group 3.75% ($p < 0.05$). Thus, if only based on the characteristics of obstetric history it will be difficult to identify APS patient among RPL population.

3.3. Features of the aCL and LA antibodies in RPL population

3.3.1. Type of antiphospholipid antibodies in RPL patients

Antibody type	1st test			2nd test	
	Negative	Positive	Positive rate%	Positive	Rate% (n=301)
LA	284	17	5.65%	2/17 (11.76%)	2/301 (0.66%)
IgM aCL	237	64	21.26%	27/64 (42.18%)	27/301(8.97%)
IgG aCL	287	14	4.5%	6/14(42.86%)	6/301(1.99%)
Total		95*		35/95**	

True positive rate of IgM aCL accounted: 8.96%, IgG aCL: 1.87% and LA 0.37%. Continuing positive test of IgM and IgG aCL respectively are 42.18% and 42.86%. Mean while, false positive rate of LA is 88.24%.

3.3.2. Factors that influence aCL antibodies and LA

Gynecological inflammation factors appear to increase in IgM aCL possitive test in the first tme (OR = 1.92 CI 1.10 to 3.36). HbsAg positive increases the chance of possitive IgG aCL at the first test (OR = 7.8 CI 2.17 to 27.99). In the second test, both gynecological inflammation and HbsAg-positive did not influence to the presence of both IgM and IgG aCL.

301 patients participated in the study were pregnant at the time off being tested. Transient positive rate of accounted for 88.24%.

3.3.3. Value of anticardiolipin antibody

Antibody concentrations	Number of patients	$\overline{X}$ ± SD	Minimum value	Maximum value
IgM 1st	64	12.91±6.61	7.5	48.4
IgM 2nd	27	12.65±3.61	8.1	19.8
IgG 1st	14	23.48±11.72	14.0	48.0
IgG 2nd	6	22.01±8.89	14.2	30.0

Positive values of IgM and IgG aCL < 40 units MPL and GPL.

In each patient, the values of aCL IgM in two tests are no linear correlation. Similarly, IgG aCL had the same relation.

3.4. To assess the effectiveness of treatment regimens of aspirin and lovenox for patients suffering from RPL acquired APS

3.4.1. Results of treatment

Patient groups	Negative	positive 1 time	positive 2 times	p
Fetal born alive n=217	135 64.29%	51 89.47%	31 91.18%	<0.001
Fetal miscarriage, fetal death n= 84	75 35.71%	6 10.53%	3 8.82%	
Total n=301	210 (100.00%)	57 (100.00%)	34 (100.00%)	

Time of evaluation at the end of pregnancy: fetal born alive or dead.

Birth weight of groups RPL suffer APS (2796.57 ± 605.68g) lower than that non suffering APS group (3059.75 ± 523.06g) ($p < 0.05$).

3.4.2. Side effects and complications of the treatment regimen

There were no cases of abnormal bleeding being seen in treated patients.

Element coagulation	Number of patients	Value		
		$\overline{X}$ ± SD	Smallest	Biggest
Platelet	91	241.78±58.94 G/l	140	402
Prothrombin	91	98.08±9.81% (11,4 s)	71% (12.6 s)	109% (11.2 s)
Fibrinogen	91	4.16±0.85 g/l	2g/l	5.6g/l
APTT	91	27.3± 0.56s*	26	29

9/91 cases had abnormal coagulation elements. 5/9 patients had low platelet results. The minimum value of platelet is 140 G/l.

Chapter 4: DISCUSSION

4.1. The incidence of APS in RPL

According to Sydney 2006 criteria, the patient is considered positive for the aPL must be tested two times separated by at least 12 weeks and the results are positive, be considered truly antiphospholipid antibodies and really suffering APS. In this study, the number of patients were positive after 12 weeks 2 times with one of two types of antibodies aCL and LA is 34 patients, accounting for 11.29% in whole population. Percentage of APS in RPL population in this study is

similar to the figures published in the world: P. Fishman 5% - 15% or Peter A 9-19%.

In previous studies of Vietnam on RPL and APS, patients are often not fully tested two types of antiphospholipid antibodies is LA and IgG and IgM aCL. Or if the patient has been tested both antibodies, they are not guaranteed to be tested twice when the first test was positive. Therefore, the published results of previous studies often give positive rate with very high aPL's incidence: Le Thi Phuong Lan (2011) gives the percentage of aPL positive up to 56%. Research Cung Thi Thu Thuy (2012) identified positive rate with up to 29.9% for only aCL. 2 studies were cross-sectional study should also have yet to come up with positive rate of aPL antibodies twice. With 11.29% miscarriage rate consecutively acquired APS, we would like to highlight just some of the objects really need to try testing for antiphospholipid antibodies (standard Sydney 2006) were:

- Patients consecutive miscarriages 2, 3 times or more and less than 10 weeks gestational age miscarriage.

- Or the case of miscarriage, fetal death after 10 weeks.

- Or early severe preeclampsia, fetal intrauterine growth retardation, premature.

4.2. Features obstetric history

Obstetric history includes information such as number of miscarriages, abortion time, the number of children living in RPL group suffering and not suffering from APS did not differ so causes the user to APS's consecutive miscarriages disease based primarily on tests APL.

4.3. Features of the aCL and LA in RPL patients

4.3.1. Ratio aCL and LA in RPL patients

In 301 RPL patients, the number of 2 times positive aCL accounted for 33/301 and 2/301 accounted for LA antibodies (a dual-positive patients both with IgG and IgM aCL in test 2 times). Thus, the aCL was predominant antibody while LA is not common in RPL. The results of this study are also similar with the statement of Lockshin that aPL that lead to RPL is aCL. Conversely, if positive, LA related to abortion in the second trimester than the first trimester. To compare with results of 1200 RPL patients in the study of Jaslow. The author also examined aCL and LA, 2 positive rate of antibody in the study population was 15.1% and 3.6%. Results of Heilmann showed 2 times positive rate of aCL is 16.7%, LA is 3%, positive for both antibodies was 6.4%.

4.3.2. Factors that influence the aCL and LA

Transient positive rate in this study were 57 patients accounted for 62% of the patients were positive for the first time. The faut positive cases may be due to factors such as infection, viral infection or some drugs that has been proven by numerous studies worldwide. The results of this study indicate that the presence of IgM aCL in the first test was related to genital infection, while IgG aCL positive at the first test related with the HbsAg positive. Therefore, the clinician should note the patient tested twice to determine precisely the real APS patients, eliminating false positive cases, avoid prolonged treatment unnecessarily.

In 301 patients, the positive rate of IgM aCL at the first time is highest 64/301 patients (representing 21.26%), IgM aCL positive in 2nd test is also high: 27/64 patients (42.18%). Whereas positive LA in second test is 11.76% rate, the false positive is 15/17 cases (88.24%).

Due to RPL is involving with aCL more than with LA and because the patients of this study were pregnant should clotting factors of the mother also change results in tests for LA is not exactly. This finding is similar with Nguyen Anh Tri's comment: "In pregnant women, the LA screening tests are often confused, no longer accurate because the concentration of clotting factors change, resulting in the normal limit coagulation tests including also altered APTT".

So LA laboratory confirmation should be carried out before pregnancy to ensure accuracy. In contrast, quantitative test IgG and IgM aCL can be made at the time before pregnancy or early in pregnancy that results are reliable.

With a detection rate IgM and IgG aC is mainly in RPL populations, clinicians may apply to test for aCL if negative then continue testing LA, the moment at is the most sensible test before pregnancy.

4.3.3. The value of the anticardiolipin antibody tests in 2 times

In 78 patients who were positive for anticardiolipin antibody IgM type (64 patients) and IgG (14 patients) in times of testing 1, the average value of the IgG aCL is 23, 48 units GPL and IgM aCl is 12.91 MPL units. The average value of the IgG aCL and IgM aCL of the 2nd test times are 22.01 and 12.65 units.

In the study of Jaslow, the authors selected only positive threshold greater than 20 GPL and MPL unit is equivalent to the average positive value of this research. Positive rate of aCL in the study was 15.1% relatively consistent with our results.

Cung Thi Thu Thuy (2012) has focused analysis anticardiolipin antibody values over 303 RPL and built percentile line indicates the value of IgM aCL and IgG aCL. Positive mean level (equivalent to a 50

percentile lines) of IgG and IgM aCL were 18.4 unit and 10.90 unit. Compared with the results of Cung Thi Thu Thuy, average values at 1st and 2nd test of IgG and IgM aCL of this study are higher.

Sydney 2006 standard applies to all APS pathologies of various subjects so IgG and IgM aCL rules have above-average positive, ie greater than 40 units. Maybe in the field of obstetrics or pathological RPL in particular, aCL positive status at a high level is not common, more common is positive in low and medium level. However, the treatment of average level positive cases is very necessary for life to improve pregnancy rate.

An important feature of the aCL observed in this study were: positive value in two attempts of each one patient had no linear correlation. Therefore, patients testing positive for the first time in low or high though still have the 2nd test, the new findings are positive patients 2 times, really antiphospholipid syndrome.

4.4. To assess the effectiveness of treatment in pregnancy women with a history RPL suffuring APS

There are two main treatments for RPL patients suffering from APS.

Direct treatments to reduce the production of antibodies, by acting on the immune system of the body. Medicines used for this method is corticoide and intravenous immunoglobulin. Treatment with corticoide have no higher effective treatments by anticoagulants mean while that cause much fewer side effects. Treatment with corticoide hardly be indicated for patients with APS any longer.

Treatment with immunoglobulin markedly effective in cases of secondary APS, the high cost of treatment therapies continues to reduce the chance of using it.

Only aspirin and low molecular weight heparin (LMWH) are most commonly used, has been demonstrated in numerous studies are highly effective when combined together. As recommended by the American association of Obstetricians and Gynaecologists and the Royal colledge of Obstetricians and Gynaecologists, we choose combination therapy of low-dose aspirin 100 mg combination with low molecular weight heparin (Lovenox) with prophylaxis dose 20 mg/day for the treatment of patients positive for one of the 3 types of IgG aCL or IgM aCL or LA. This is also applicable to the study of the Ministry of Health: "Analysis the diagnostic process and treatment regimen antiphospholipid syndrome in RPL" was adopted and deployed at the Central Maternity Hospital in 2012.

4.4.1. Duration of treatment

91 patients were treated with combination regimen of low-dose aspirin and lovenox were divided into 2 groups: group 1 - transient positive: 57 positive patients and group 2 – actual APS 34 patients. The average duration of treatment of transient positive group was 12 weeks. and APS group is 26 weeks.

4.4.2. Effective treatment

Effective treatment of the study were evaluated at two times: at the end of first trimester and late pregnancy. At the end of the first trimester of pregnancy, fetal development of APS group was relatively high 94.12%, while this number of the APS negative group was 64.76% fetal development ($p < 0.01$). Two cases of miscariage in APS group are pregnant patients come too late at 8 weeks of gestation even though they were treated with both aspirin and lovenox the fetus could not develope. 94.12% fetal development through the first trimester was very high figure shown if diagnosed, these RPL acquired APS can

completely cure. Study of Mo (2009) treated with aspirin and 20 mg enoxaparin, fetal development rate over the first trimester was 80%. All 7 patients who did not develop during pregnancy of Mo study appear in the first trimester of pregnancy, there is no case of fetal death or miscarriage after 12 weeks. At the end of pregnancy, live birth pregnancy rate in this study was 91.18% higher than the results of MO live birth pregnancy is 80%, this difference was not statistically significant, $p > 0.05$. Results of the two studies were similar by applying the same treatment regimens: low molecular weight heparin dose of 20mg/day low dose combination with aspirin 100 mg / day. Compared with 71% live birth pregnancies in the study of Backos and Rai, this study's result was significantly higher ($p < 0.05$).

Backos and Rai patients treated under combination therapy with aspirin and natural heparin and low molecular weight heparin. Natural heparin is less effective than low molecular weight heparin because LMWH are likely tied directly to the aPL, inhibit the activity of these antibodies, preventing coagulation phenomena. In addition, LMWH also inhibits complement activation which inhibit the activity of aPL, therefore, that LMWH has better efficiency in pregnancy. In this study, only one case of stillbirth at 32 weeks, despite being treated with anticoagulants from 5-week-old fetus. According Hailmann, up to 30% of cases treated with heparin combination with aspirin but still not developed fetus, in this case the authors have proposed combination with aspirin and heparin immunoglobulin.

4.4.3. Complication - the side effects of the treatment regimen

For fetuses, heparin does not pass through the placenta should not have a direct impact on the fetus. Ginsberg and Hirsh's research (1998) shows that high-dose aspirin use with > 150 mg/day may affect fetal risk.

For mothers, the tracking process includes examination and blood tests and coagulation formula basically for patients 1 weeks during the first month and then monthly to detect the condition during which the blood grandchildren treatment.

4.4.3.1. Complications at clinical level

The study did not find any cases of abnormal bleeding during pregnancy, during labor or the postpartum period on 91 patients treated with lovenox and aspirin. Because the therapeutic dose in the studies was low dose lovenox 20 mg/day should not hemorrhagic complications appear.

Expression bruised skin around the navel at heparin injection sites are unique signs appear in the patient during treatment. But the bruised skin nodules is without adversely affecting health and without special treatment.

Having accounted for 9.89% (9/91 patients) had signs of epigastric pain, belching, heartburn. These symptoms are manifestations of gastritis level, an undesired effects when using aspirin. Treatment by discontinuing aspirin, still the treatment lovenox, and additional medication immediately wrap the stomach lining, no patients had gastrointestinal bleeding.

4.4.3.2.The disturbances in the clinical level

Among 91 patients treated with anticoagulants, 9 patients with coagulation test results in mild disorders proportion 9,89%. The disorder mainly thrombocytopenia (5/9 patients). However, the average value of platelets, prothrombin and fibrinogen of 91 patients in this study is similar to 254 healthy pregnant women in the study by Phan Thi Minh Ngoc. Treatment with LMWH simple monitoring tests than heparin natural treatment lot, no need to test or prothombin APTT and

fibrinogen, just detecting the status of thrombocytopenia. LMWH and thrombocytopenia less than natural heparin. The average value of platelets in this study was 241.78 ± 58.94 G/l equivalent of platelets results from normal pregnancy in the first quarter was 223.27 ± 45.70 G/l and third quarter was 203 ± 63.93 G/l. The smallest value of platelet patients in the study was 140 G/l lower than the physiological constants but no cases had platelet counts fall below 100 G/l, the degree thrombocytopenia players can lead to bleeding.

Timing expressed thrombocytopenia in 5 different patients, but all were later than seven weeks since started using heparin. Heparin can cause thrombocytopenia after 7-14 days of use, but this study used low-molecular-weight heparin is very low dose of 20 mg/day should be rare complications can appear later and affordable. Nine patients had platelet counts decreased and other disorders of medical tests may be temporarily interrupted treatment for 2 weeks and quantify the platelets and clotting factors underlying. The test results of the patients are back to normal limits even after stopping therapy 2 weeks and the patient is continuing treatment Lovenox combination aspirin regimen on. This result showed that Lovenox low dose and low-dose aspirin is relatively safe so the mother and fetus.

4.5. Late complications of APS impact on the second and third trimester of pregnancy

APS cause fetal viability below 10 weeks gestational age. In the second and third quarters, APS causes late stillbirth, oligohydramnios, premature birth, preeclampsia early. Research by Oshiro (1996) on the 333 pregnancy of 76 patients with APS showed that 50% of deaths in the second trimester and the third pregnancy. Research by Heilmann L. (2003) also showed that the incidence of complications in the second

and third trimester of pregnancy in patients suffering from APS consecutive miscarriages accounted for 50% of cases.

In 301 patients with a history of RPL, we recorded 10 cases with a history of stillbirth after 12 weeks of unknown cause in which groups with a history of suffering from APS late stillbirth is 14.71% , 9.03 times higher than non-APS patients ($p < 0.001$). In the current pregnancy, the results showed that the incidence of late morbidity of APS group was 47.06% the equivalent results of Heilmann L (1996), Oshiro (2003) was 50%. Compared with no questions APS, incidence of positive group 2 times higher than 5.52 times, $p < 0.001$. Thus, it is possible for the patient population consecutive miscarriages, aPL antibodies were preexisting row has caused miscarriages and stillbirths late before. To this pregnancy, the antibody continues to clot at the Circuit of thorns vegetables, threatening the development of the fetus, in accordance with the statement of Bertolaccini ML: more than 50% who tested positive for antibodies APL will be developing or will develop pathologies related to APS for 10 years.

The study results also showed that the average birth weight of mothers infected groups consecutive miscarriages APS was (2796.57 ± 605.68g) lower birth weight do not suffer APS group 3059.75 ± 523. 06g ($p<0.05$). Although having success incidence of live birth rate up to 91,18%, lower birth weight was a matter that RPL mother had to cope up. They need to be closely monitored.

In this study, there is only one in the group of patients suffering from APS consecutive miscarriages treated lovenox and aspirin after 5 weeks pregnant to 30 weeks continuously detected retarded fetal condition in uterus. Patients were hospitalized for treatment and better

monitor but still use Lovenox doses of 20 mg/day after 2 weeks of pregnancy should die. Both the 8 patients with fetal growth retardation condition in the womb, when this complication occurs after 26 weeks. Does the use of Lovenox in doses of 20mg/day for pregnant helps develop well through the first quarter of pregnancy, but not enough for continuous fetal development in the third quarter.

American Society for Reproductive Medecine also recommended: 81 mg dose aspirin therapy and heparin 100,000 unit rate only increased fetal life but does not eliminate all the complications of preterm labor, premature rupture of membranes, fetal growth retardation uterine. Want to reduce the late complications of APS syndrome need to use high - dose heparin 2mg/kg in 24 hours, equivalent to the dose of 80 mg/day. The monitoring and early detection of diseases later in APS patients with a history of miscarriages in a row is very important, detection and early treatment will improve living fetus.

CONCLUSION

1. Characteristics of obstetric history and anticardiolipin antibody and lupus anticoagulant in RPL patients

1.1. APS is the most common cause in RPL accounted for 11.29% of patient populations in this research.

1.2. Characteristics of obstetric history of patients in non APS and APS group are no different .

1.3. In the population of RPL patients, anticardiolipin antibody IgM is the most common type accounting for 8.97%, lupus anticoagulant antibodies having accounted for only 0.66%.

1.4. The concentration of IgM aCL and IgG aCL in RPL is in the average level in 2 times the test.

1.5. The relationship between the value of IgM aCL and IgG aCL in in 2 attempts is not linear. 2nd tests for positive cases in the first try to exclude transient cases positive is necessary.

1.6. Gynecological infection and positive HbsAg increased risk of transient IgM and IgG aCL. Pregnancy is a special condition that increases the rate of false-positive lupus anticoagulant test.

2. Treatment

2.1. Treatment of patients suffering from APS with regimen of aspirin of 100 mg/day and low molecular weight heparin dose of 20mg/day has live born rate of 91.18%.

2.2. Treatment regimen is safe for mother and child, there is no case of bleeding during pregnancy, during labor and postpartum.

2.3. In patients treated with 2 anticoagulants, the thrombocytopenia proportion accounted for 5.49%, the minimum value of platelet is as 140 G/l, the mean value of platelet of 241.78 ± 58 patients,

2.4. Although the anticoagulant therapy increased the rate of the live born rate, the incidence of the APS disease at second and third trimester still accounts for 47.06%.

2.5. The average birth weight of APS groups is 2796.57g ± 605.68g lower than that of non APS group 3059.75g ± 523.06g.

RECOMMENDATIONS

1. Patients with recurrent miscarriage should be examined and explored all tests to find causes, including antiphospholipid antibodies before pregnancy.
2. Continue research to find appropriate treatment regimen to reduce late complications of antiphospholipid syndrome in RPL populations.
3. Learn the role of β2 glycoprotein antibodies in RPL.
4. Expand research antiphospholipid syndrome in population of uterine growth retardation, late miscarriage, premature birth, early severe preeclampsia.