Antiphospholipid Antibodies and Growth Retardation in Intrauterine Development

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Abstract: The aim of this study was to evaluate the efficacy of prophylaxis using low-dose non-fractioned heparin and aspirin in the prevention of intrauterine growth restriction and low birth weights in patients suffering from antiphospholipid antibody syndrome. Intrauterine growth retardation and birth weights of 34 gestations involving 28 women with histories of multiple miscarriages and elevated antiphospholipid antibody levels were evaluated in a prospective study in the period from April 1988 to July 2004. A control group was formed of 39 women without previous history of miscarriages over a total of 40 gestations. Intrauterine growth retardation was considered when the weight of the newborn baby was below the tenth percentile for gestational age according to the fetal weight chart. Diagnosis of antiphospholipid antibodies was achieved using the ELIZA test to measure the IgG and IgM immunoglobulin levels. Evaluation of lupus anticoagulant was performed using the activated partial thromboplastin time (aPTT). Women suffering from antiphospholipid antibodies underwent prophylactic treatment during gestation with low doses of acetylsalicylic acid (100 mg daily) associated to low doses of subcutaneous heparin (5000 IU twice daily). The non-paired Student t-test, Fisher Exact and Mann-Whitney tests were used for statistical analysis with an a error of up to 5% considered acceptable. A statistically higher number of newborns suffered intrauterine growth retardation and low birth weights in the study group than in the control group. In conclusion, children of mothers suffering from antiphospholipid antibody syndrome, even those undergoing prophylactic treatment with low-dose non-fractioned heparin and aspirin, are associated to intrauterine growth retardation and low birth weights.

Introduction

Antiphospholipid antibody syndromes (AASs) during pregnancy are characterized by the presence of antiphospholipid antibodies associated to miscarriages and complications such as preeclampsia, intrauterine growth restriction or placental insufficiency [1–4]. AASs constitute a heterogeneous group of circulating auto-antibodies against anionic phospholipids with anticardiolipin antibodies, venereal disease reaction of Lues (VDRL) and lupus anticoagulant being the most important [2–5].

Preeclampsia and placental insufficiency occur in around 50% of non-treated patients and the success rate of prophylactic treatment with heparin or aspirin in respect to this is approximately 70% [1]. Foetal death in AASs is frequently preceded by intrauterine growth retardation (IUGR), oligohydramnios and abnormal heart beats indicating hypoxia. All these symptoms may be caused by utero-placental insufficiency [5]. The association of IUGR with AAS has been reported by some studies [6–9], however in others this association was not confirmed [10–12].

The objective of prophylaxis during pregnancy is to attempt to normalize the conditions of the patient thus the aim of the current study was to evaluate the

efficiency of prophylaxis with non-fractioned heparin associated with low doses of aspirin in the prevention of IUGR and low birth weight linked to antiphospholipid antibody syndrome.

Method

IUGR was studied in a prospective randomized study of 34 pregnancies of 28 women with histories of two or more miscarriages. All pregnancies were followed up at the Pre-natal Service for High-Risk Pregnancies in the Gynecology and Obstetrics Department of the Medical School in São José do Rio Preto (FAMERP) during the period from April 1988 to July 2004. All patients were positive for antiphospholipid antibodies (anticardiolipin antibodies or lupus anticoagulant). A randomized prospective control group was formed of 40 pregnancies of 39 apparently healthy women without history of miscarriages and who were not taking AAS.

Foetal growth restriction was considered when the weight of the newborn baby was below the tenth percentile for gestational age as shown on the foetal weight chart [4]. Diagnosis of anticardiolipin antibodies was done according to IgG and IgM serum titres measured in one or two ELISA tests (INOVA Diagnostics San Diego). Measurement of the lupus anticoagulant was done using activated partial thromboplastin time (aPTT).

Table 1 – shows the birth weight in the two groups

Patient	Group study	Control group	Patient	Group study	Control group
1	2980	3465	21	3070	3445
2	1750	2380	22	3895	2800
3	3290	3150	23	3220	2890
4	3195	3040	24	3950	3690
5	2710	3890	25	2660	3450
6	2265	3040	26	2725	3255
7	1830	2905	27	1615	2270
8	2750	3070	28	3140	3015
9	2415	2900	29	3270	3235
10	3180	3115	30	2720	2970
11	2960	2635	31	3460	3650
12	2820	3690	32	2928	2780
13	297	3060	33	2827	3380
14	2345	3060	34	2906	3660
15	2850	3420	35		3260
16	2485	2950	36		3225
17	3470	2910	37		2700
18	4265	2400	38		3525
19	2275	3000	39		3550
20	2645	3025	40		3123

Women with antiphospholipid antibodies started prophylactic treatment after laboratorial confirmation of the pregnancy taking low doses of acetylsalicylic acid (100 mg/day) associated with low doses of subcutaneous heparin (5000 IU twice daily).

Statistical analysis was achieved utilizing the non-paired student t-test, Fisher exact and Mann-Whitney tests with an alpha error of 5% considered acceptable (p-value < 0.05).

Results

IUGR occurred in 11 (32.3%) patients of the Study Group and in only one (2.5%) of the Control Group giving a significant difference (p-value < 0.0008) according to the Fisher exact test.

The mean weights of the newborn babies were 2798.9 grams in the Study Group and 3124.5 grams in the Control Group (Table 1) giving a significant difference (p-value < 0.04) according to the student t-test and Mann-Whitney test.

Discussion

The current study shows that in spite of the use of prophylaxis with heparin and aspirin provided to all women in the Study Group there was a reduction in the intrauterine growth and lower birth weights of newborn babies of mothers suffering from AASs in relation to the infants of women without AASs. Publications stress the necessity of prophylaxis for these patients thereby improving the outcomes of pregnancies with reduced maternal and foetal morbidity [4, 13].

In a prospective study using 5000 IU of heparin associated with aspirin, 15% of babies of mothers suffering from AASs were born with low weights for gestational age [4]. Experimental data also describe IUGR and placental insufficiency in rats treated with purified IGG [14, 15]. Other studies reported the existence and results of IUGR similar to our findings [1, 16]. There are warnings about the use of corticoid for prophylaxis which is associated with IUGR [17–19]. IUGR is associated to an increase in the morbidity and mortality compared to normal foetuses [20].

These data reflect the lack of consensus on the issue and suggest that further research to determine the real cause of low birth weight and IUGR are necessary. Prophylaxis was useful in the prevention of miscarriages however in respect to IUGR and low birth weight it did not prove to be efficient. It is also important to question if aspirin may interfere in the birth weight and thus further studies are necessary to elucidate this question.

Conclusion

Newborn babies of mothers suffering from antiphospholipid antibody syndromes are associated with IUGR and low birth weight and prophylaxis with non-fractioned heparin and low doses of aspirin does not totally eliminate this complication.

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