Effect of treatment on cases testing positive for APA: A Prospective Study

Pankaj Desai, Monali Desai, Deepti Mody, Reena Anand
Dept. of Obst. & Gynecology, Medical College & S.S.G. Hospital Vadodara – 390001

Summary : 154 subjects testing positive for APA, were given immuno suppressive &/ or immuno modulatory treatment. Low dose aspirin and low dose prednisolone were the pillars of the treatment protocols. In the group where treatment could be given pre conception as well as post conception, full term delivery rates achieved were 88.3%. In the group where only post conception treatment could be given, full term delivery rate was 72.3%. There was a significant reduction in recurrent missed abortions, S.B., IUGR as well as pre eclampsia remote from term following this treatment protocol.

Introduction:

Anti Phospholipid Antibodies (APA) are clinically very important auto-antibodies. This is due to a strong association found between them and occurrence of adverse obstetric outcomes. These outcomes include pre-eclampsia of early onset (Branch et al 1989), IUGR (Lockshin et al 1985), placental abruption (Birdsall et al 1992) and missed abortions as well as recurrent still births (Harris 1987). Three type of APA are clinically important. These include

- Anti Cardiolipin Antibodies (ACA)
- Lupus anticoagulant (LAC)
- Biologically False Positive Test for syphilis (FPSTS)

All the three are inter related. In this study, we have measured ACA. We are presenting the effect of treatment, prospectively studied on these cases.

Material & Methods:

This study was carried out in Unit III of the Dept. of Obst. & Gynecology, Medical College and S.S.G. Hospital, Baroda. Two hundred and sixty six consecutive cases with specified adverse obstetric outcomes were included in this study. These outcomes include:

A) Recurrent (>2) missed abortions
B) Recurrent (>2) still births
C) Pre- eclampsia remote from term
(Before 28 completed weeks of gestation)
D) Unexplained Abruptio placenta
E) Unexplained IUGR

These cases were subjected to APA testing. Facility for this testing was not available at the institution so help was taken from the private sector in the city, after taking due permission. ACA values were:

	Value in GPL unit
• Insignificant or Negative	<10
• Low Positive:	10-20
• Moderately positive	20-100
• Strong Positive:	>100

Of these 226, 42 were either lost to follow up or refused investigations after agreeing initially. Thus, only 184 cases could be finally analyzed as part of the study. There were two portals of entry in this study.

- Portal A (Group A). These were cases in whom an adverse obstetric outcome had occurred and were now having early pregnancy (< 8 wks.). These cases were investigated for APA. Those testing positive were subjected to specified protocol of treatment.
- Portal B, (Group B): These were cases who gave past history of such an adverse obstetric outcome and sought investigations. These subjects were in interval period when enrolled. Those testing positive were subjected to treatment protocol as below.

For low and moderate positive.
Low dose aspirin was given in a dose of 75-mgm/ day for three months. This was in the interval period. Conception was advised and planned immediately thereafter. Aspirin was restarted in the same dose at 12 wks. and continued upto 36 wks. or upto a recurrence of adverse outcome whichever was earlier.

For High positive:
Low dose prednisolone (10 mgm/ day) for three months

followed by pregnancy. During pregnancy, low dose aspirin from twelve weeks to 36 wks. or upto a recurrence of adverse obstetric outcome whichever was earlier.

Those subjects (Group A) who came when already pregnant could not be given pre pregnancy treatment. They were given the post pregnancy protocol only.

All subjects were given Inj HCG 5000 I.U. weekly from the diagnosis of pregnancy (Group B) or from enrollment (Group A). This was given until the pregnancy reached 12 wks. Inj. Immunoglobulins (Bharglob – Bharat Serums Ltd.) in a dose of 2 ml. intramuscularly of 16.5% strength, every twenty first day. This was continued until 36 wks. of pregnancy.

This treatment of protocol is tabulated in Table I.

Table: I

Treatment Protocol

For group (A)	**For Group (B)**
~ Inj HCG 5000 I.U. every Wkly. till 12 wks.	In Low & Mod. Positive Tab. Aspirin 75 mgm. For 3 months allow conception. Rest of protocol like group (A)
~ Inj Immunoglobulins 16.5% of 2ml. every 21 days till 36 wks.	In High positive -Tab. Prednisolone 10 mg/day for 3 months → allow conception Rest of the protocol like group(A)
~ Tab. Aspirin 75 mgms./ day from 12 wks. till 36 wks.	

All results were carefully documented and analyzed to draw valid conclusions. Standard chi-square test of statistical analysis was used. Statistical indices were cross-checked on SPSS software.

Results:

In all, there were 184 cases whose investigations and complete follow up could be done.

Table – II

Distribution of APA positive & -ve cases

	Positive		Negative		Total
	No.	%	No.	%	
Gr. A	94	83.2	19	16.8	113
Gr. B	60	84.5	11	15.5	71
Total	154	83.6	30	16.3	184

As shown in this table, 113 subjects were in group A. These were investigated when they were already pregnant. Of these, 94 (83.2%) tested positive. 19 (16.8%) tested negative for APA and were therefore not subjected to the treatment protocol specified above. In Group B, 60 out of 71 (84.5%) tested positive for APA. Group B included subjects who were investigated in the interval period. They could be given pre-conception treatment as well.

Table-III

Effect of Treatment in Group (A) [N=94]

	Pre treatment		Post Treatment	
	No.	%	No.	%
❑ Full term del.	00	00.0	68	72.3
❑ Missed abortion	51	54.3	09	9.6
❑ S.B.	34	36.2	08	8.5
❑ IUGR	32	34.1	11	11.7
❑ P.E. Remote From Term	08	8.5	02	2.1
		[P<0.001]		

As shown in table III, 72.3% subjects had full term delivery. Total number of subjects is more than 94, because some subjects had more than one adverse outcome. Incidence of missed abortions, still births, IUGR and pre-eclampisa remote from term all decline very significantly after treatment (P<0.001).

Table – IV

Effect of Treatment in Group (B) [N=60]

	Pre Treatment		Post Treatment	
	No.	%	No.	%
❑ Full term del.	00	00	53	88.3
❑ Missed	34	56.6	00	00
❑ S.B.	18	30.0	02	3.3
❑ IUGR	08	13.3	03	5.0
❑ P.E. Remote from Term	16	26.7	02	3.3
		[P<0.001]		

This table depicts obstetric outcome in cases when both pre conception as well as post conception treatment could be given. Highly significant results emerge (P<0.001). The incidence of pregnancies reaching full term rose to 88.3% and incidence of S.B., IUGR and preeclampsia remote from term plummeted from 30%, 13.3% and 26.7% to 3.3%, 5.0% and 3.3% respectively.

Discussion:

Anti phospholipid group of antibodies have been responsible for many adverse obstetric outcomes. Most of these are explainable by their tendency to produce vasculopathy at feto-maternal interface. The successful treatment of women with APA positive originally contained corticosteroids in immuno-suppressive doses (Prednisolone 40 – 60 mgms./day) and low dose aspirin (75 mgms./day) – Lubbe et al (1983). A variety of therapeutic interventions and protocols has been described since this report. In most of these aspirin, corticosteroids, heparin, and immunoglobulins have been the mainstay. In the present study, low dose aspirin, low dose corticosteroids, immunoglobulins and HCG have been used. Lockshin (1989) reported significant reduction in still births and missed abortions with these agents. Similar results have been found in the present study as well. Role of corticosteroids during pregnancy has indeed been debatable (Cowchok et al 1992). However, in our protocol corticosteroids have been given pre-conceptionally and in low doses. Peacemen et al (1993) has shown the effect of immunoglobulin fraction in APA cases producing the undesirable obstetric outcomes. They have suggested that low dose aspirin produces an immuno-modulated state. This helps in thwarting the attempts of APA in destroying the pregnancy. It also explains better results obtained when preconception treatment could also be given as in Group B cases. These cases had a high (88.3%) full term delivery incidence as compared to 72.3% found in Group A. The difference was statistically significant (Chi~square value = 5.0904 $P < 0.02$, significance at 2%)

The difference in obstetric outcome pre treatment and post treatment on statistical testing is all showing $P<0.001$. Nevertheless, obstetrics at times, may not follow all rules of statistics. This is important when considered in the light of observations of Carp et al (1990) who found that in any given case of RSA (Recurrent Spontaneous Abortions), the chances of spontaneous resolution are 70%. Now, Group A had a full term delivery rate of 72.3%. Though this is numerically higher than 70% statistical tests can't be done here for very obvious reasons. However when this figure soars to 88.3% in Group B than this result in well beyond a mere chance observation. It can therefore be safely concluded that when pre as well as post pregnancy treatment protocols could both be given to the patients, chances of having a favorable outcome is scientifically bright.

Human Chorionic Gonadotropin (HCG) like progesterone in recurrent pregnancy loss, remains an evergreen controversy. The rationale of including it in our protocol is two folds:

A In our prospective study (Desai P et al 1995) we have scientifically demonstrated its efficacy in increasing resolution rates significantly in cases of recurrent spontaneous abortion

B Carp et al in 1990 have shown that HCG preparations are always mixed with growth factors, antidiotypic antibodies and other immune active components. It is likely that HCG itself might be acting as an antigen. In the light of this information, HCG seems to have an immune-endocrinal basis for its activity. In fact, a recent report hints at an amazing structural similarity between these immune growth factors and that of HCG. (Hao Wu et al, 1997)

These two reasons made us include HCG in our protocol. It is not our endeavor to pinpoint which agent singly acted to get good outcomes. However, it is the entire protocol of administration of different agents that have acted to produce satisfactory results.

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References:

1 Branch D.W., Andres R, Digre K.B., Rote N.S. and Scott J.R.: Obst. & Gynec 73: 541, 989.
2 Birdsall M, Pattison N, Chamley L: Aust. NZ Jr. Obstet. Gynec: 32: 328, 1992.
3 Carp H.J.A., Todar V. and Mashiach S.: Obstet & Gynec. Survey: 45: 657, 1990.
4 Cowchock F.S., Reece E.A., Balaban D, Branch D.W.: Am. Jr. Obst. & Gynec.: 166: 13,8, 1992.
5 Desai P., Desai M., Manjunath A.P.: J.Obst. & Gyn. India: 45: 169, 1995.
6 Hao Wu, Lustbader J.: Biomedical Frontiers, 5,1,1997
7 Harris E.N.: Brit J. Rheumatol: 26; 324: 1987
8 Lockshin MD, Druzin M.L., Goeis N.; N. Engl. J. Med.: 313: 152, 1985.
9 Lockshin MD, Druzin ML, Qamar T., Am. J. Obst & Gyn: 160: 439, 1989.
10 Lubbe W.F., Butler W.S., Palmer S.J.; Lancet: 1: 1361, 1983.
11 Peaceman A.M., Rehnberg K.A.: Am J. Obst. & Gyn. 169: 1403, 1993.