Trombophrophylaxis throughout pregnancy in women with previous history of recurrent miscarriages of unknown aetiology

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Summary

The purpose of this prospective preliminary clinical study was to assess the efficacy of thromboprophylaxis throughout pregnancy in women with a history of unexplained first trimester recurrent miscarriages. From the 53 patients originally assigned to the study 15 were excluded. The remaining 38 were treated with low molecular weight heparin (LMWH-natroparine calcium 0.3 ml twice daily) and low dose aspirin from the day the fetal heart motion was detected until the 37th week or earlier at the onset of premature labor. Among the patients treated (n = 38) thrombophilia screening was positive in 16 patients and in the remaining 22 no causative factor was detected. The overall success rate (viable pregnancy ≥ 24 weeks) was 92.2% with no significant difference between patients with positive or negative thrombophilia screening. The most significant complications were: preeclampsia (21%), IUGR (26%), placenta abruptio (5.2%), injection site haematoma (44%) and skin reaction (15.7%). No abnormal bleeding was observed during vaginal or caesarean section. The results of this study suggest that thromboprophylaxis during pregnancy, which has already been successfully tried in patients with recurrent miscarriages with a causative factor, may be similarly effective in patients with such a pregnancy complication but of unknown aetiology.

Key words: Recurrent miscarriages; Thromboprophylaxis.

Introduction

Recurrent spontaneous abortion, a controversial clinical problem in reproduction, occurs in about 1% of women of reproductive age. In the majority of cases [1] there is no definite causative factor established and the various treatment modalities employed in the past, often based on unproven hypotheses, have not resolved the problem. Antiphospholipid antibodies (APA), with anticardiolipin antibodies (ACA) and lupus anticoagulant (LA) are the most studied and appear to be strongly associated with recurrent miscarriages, thrombosis and thrombocytopenia [2]. They have also been associated with early onset preeclampsia, intrauterine growth retardation, placental abruptio and infertility [3-6]. Although both ACA and LA are often detected in patients with systemic lupus erythematosous (SLE), individuals carrying these antibodies do not necessarily present the major clinical and serological features of SLE.

The fetal loss in women with APA ranges between 50% and 75% [7-9] and as high as 96% in the presence of SLE [10, 11]. The prevalence of APA among all women with a history of recurrent miscarriage (three or more), contrary to the "low risk population" (1-2%), has been reported to range between 11% and 42% [5, 11] or less than 15% according to others [12, 13].

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The mechanism of an adverse effect of ACA on pregnancy outcome may involve both implantation and postimplantation periods. Defects in the process of the first (apposition, attachment and invasion of endometrial epithelium by the trophectodem) are the most significant factors in early pregnancy loss, also implicated in the aetiological mechanism of preeclampsia and intrauterine growth retardation later on. There has been mounting evidence to suggest that APA may impair trophoblast function by binding to the cytotrophoblast cells leading to their direct injury and failure of syncytia formation [14, 15].

A cofactor required for the binding of ACA (_2GPI) was found in high concentrations on the trophoblast surface of the placentae of women with raised ACA titres, but the same was also found in others without such antibodies [16], thus indicating the existence of other causes that may also impair cytotrophoblast function and syncytia formation.

The postimplantation changes that cause adverse pregnancy outcome with fetal demise, are related to thrombogenic effects leading to decreased placental perfusion and also to mere vasculopathy [17]. This is the result of abnormal placentation, normally completed between the 6th and 18th week of gestation and characterized by intralumilar thromboses and thickening of the spiral arteries associated with fibrinoid necrosis and atherosis of the decidual vessels.

Low-dose aspirin has been shown to selectively inhibit thromboxane synthesis without affecting pro-

stacyclin production18 and its administration, in the presence of high ACA titers [19] and for the prevention of preeclampsia [20], has been associated with high birth rates, reports though not confirmed by others [21, 22]. In a similar manner, heparin (unfractionated or low molecular weight) alone, or in combination with aspirin, has also been used in the presence of phospholipid antibodies, with average to very high success rates [13] and in patients with recurrent fetal growth retardation and preeclampsia. Late commencement of the treatment however, after the appearance of clinical signs, has not been successful due to the fact that placental lesions are already extensive [20]. Low molecular weight heparin (LMWH), an increasingly attractive alternative to subcutaneous heparin, does not cross the placental barrier, is safe and offers satisfactory antithrombotic protection to both maternal and placental circulation [23].

Acquired maternal thrombophilia, mainly antiphospholipid syndrome and inherited thrombophilias, have strongly been associated with recurrent early fetal loss and complications of the second trimester like IUGR, preeclampsia, etc. For patients with such obstetric complications, it has been suggested that they be tested for markers of thrombophilia and managed accordingly, even in the absence of a history of thromboembolism [24].

The very fact though that placental thrombosis is a common finding whether thrombophilia is present [7] or not, indicates that other additional abnormal mechanisms are also responsible. These mechanisms frequently interact in such a way that the isolation of the real cause often proves extremely difficult. The above new data provide fascinating insights into the pathophysiology of the aforementioned complications including recurrent miscarriages and new opportunities for their prevention with low dose aspirin and LMWH.

The widely used immunotherapeutic treatment with paternal lymphocyte immunization and intravenous immune globulin (IVIG), following Mobray's *et al.* study in 1985 [25] has not proven effective according to several randomized prospective studies [26-28] and may even be harmful [1].

Patients with recurrent miscarriages have been successfully treated with aspirin and low dose heparin, a treatment though confined to those associated with antiphospholipid syndrome which does not represent more than 15% of all cases [6].

In view of the fact that, in the cases with a history of recurrent first trimester spontaneous abortions, regardless of the presence or not of a known causative factor (i.e. thrombophilia), the final cause of fetal demise invariably is placental microinfarction. Thus we employed the symptomatic treatment of thromboprophylaxis throughout pregnancy to all patients who presented with such a history of early pregnancy complications after proper counseling and careful monitoring during treatment.

Materials and Methods

In a prospective cohort study, 53 patients with a history of first trimester "recurrent miscarriage" were studied between 1998 and 2001 after obtaining an informed consent. Fifteen were excluded due to a diagnosed anatomical or endocrinological abnormality (Table 1). The remaining (n = 38) were put on a fixed regime of low dose aspirin (salospir 80 mg, Uni-Pharma, Greece) in combination with low molecular weight heparin (natroparine calcium, 0.3 ml twice daily subcutaneously, fraxiparine, Sanofi Winthrop Industrie, France) regardless of body weight. The treatment was commenced as soon as the fetal heart was detected by transvaginal ultrasound. Clotting mechanism tests were performed before and at regular intervals after the initiation of treatment. The treatment was interrupted at the first signs of premature labor, otherwise it was continued up to the 37th week. When thrombophilic defects, symptomatic or not, were known to be present, low molecular weight heparin was continued until three months post-partum.

Results

Table 1 shows the reasons 15 patients were excluded from the study. Eight were with gross anatomical malformations (three with Ascherman's syndrome, one of which was managed by surrogacy resulting in the birth of twins, and five with distorted uterine cavities due to previous surgery for multifibroid and bicornuate uteri), two with diabetes mellitus and high Alc levels, two with high levels of homocysteinemia allocated for alternative treatment and three cases with marked polycystic ovaries.

From the remaining 38 cases 16 were found to have evidence of acquired or congenital thrombophilia (Table 2). Thrombophilia screening [29] in the remaining 22 cases proved negative.

No abnormal bleeding was observed during vaginal deliveries or caesarean section. Comparison of bone

Table 1. — *Causes for exclusion from the study.*

Cause	Number of cases
Ascherman's syndrome*	3
Distorted uterine cavity	5
Diabetes Mellitus	2
Hyperhomosteinaemia	2
Severe PCOS	3
Total	15

Table 2. — *Patients with positive evidence of acquired or congenital thrombophilia.*

Type of thrombophilia	Number of cases
Protein S deficiency	2
Protein C deficiency	1
Factor V Leiden mutation	4
Antithrombin III deficiency	1
Lupus anticoagulant	3
Anticardiolipin antibodies (IgG)	2
Combined defect	3
Total	16

density before and after pregnancy to assess possible osteoporotic effects of the treatment was not performed as a routine. In the 11 patients who agreed to have a bone density scan during the puerperium, mineral mass was found within normal range. No fetal malformation was detected.

Discussion

According to previously reported controlled studies, preventive treatment with aspirin and dipyridamole throughout pregnancy has been tried in patients with a history of fetal growth retardation of unknown aetiology [30, 31], but low molecular weight heparin was administered only in the presence of a known contributing factor i.e., thrombophilia or in patients with a previous history of thromboembolism. In this unselected group of patients with a history of recurrent miscarriage, LMWH which does not cross the placental barrier and offers satisfactory antithrombotic protection for both maternal and placental circulation [32], was proven effective, regardless of a positive or negative thrombophilia screening test, the latter representing the majority of the cases. To exclude cases unlikely to respond (i.e., with blighted ovum or very early missed abortion), the treatment was commenced only after the detection of the fetal heart.

Supportive care alone has been associated with a success rate of up to 75% [30, 33] although this did not seem to be the case in 14 of our patients who had already undergone immunotherapeutic treatment in previous pregnancies, but without results. Furthermore, the final success rate achieved in this study protocol was significantly superior to the above-mentioned 75% success rate.

Preventive treatment throughout pregnancy from the first trimester in an unselected group of patients without evidence of thrombophilia or previous thromboembolism has not been known as a common practice before. In this study such a thromboprophylaxis, although a symptomatic treatment, proved equally effective, whether a causative factor (i.e. thrombophilia) for their previous first trimester recurrent miscarriages was detected or not. Considering that 50-75% of the cases remain of unknown aetiology, by extending the indication of this treatment to all patients with a positive history of this early pregnancy complication, after the appropriate counseling and careful monitoring throughout pregnancy, a much wider spectrum of these difficult-to-manage patients could benefit.

Table 3. — *Clinical characteristics of patients treated with low dose aspirin and low molecular weight heparin (LMWH) and pregnancy outcome (mean ± SD).*

Number of cases	38
Age (yrs)	27 ± 5 (22-37)
Body weight (kg)	62 ± 9
Number of previous miscarriages	4 ± 6 (3-12)
Week of previous miscarriages	7 ± 2 (6-13)
Commencement of treatment (gestational week)	
Aspirin*	5 ± 3.2 (-4 to 8)
LMWH•	± 0,8 (6 to 12)
Thrombophilia screening positive	16
Thrombophilia screening negative	22
Pregnancy outcome	
miscarriage	(7.8 %)
viable pregnancy	35 (92.2%)
Gestational week at birth	35,8 ± 6 (27-40)
Mode of delivery	
Vaginal	28 (80%)
Caesarean section	7 (20%)
Birth weight	
< 2.5 kg	16 (45%)
> 2.5 kg	20 (55%)*

• Treatment was started during the 6th or 7th week in all but one case at the 12th week.

* One set of twins included

Table 4. — *Complications in patients treated with low dose aspirin and LMWH for recurrent miscarriage.*

Complication	Number of cases	%
Preeclampsia	8	21
moderate	5	
severe	3	
IUGR	10	26
moderate	8	
severe	2	
Placenta abruptio	2	5.2
Injection site haematomas	16	32.1
mild	13	
moderate	3	
Skin reactions	6	15.7
local	6	
generalized	0	

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