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ORIGINAL ARTICLE



# Placenta-mediated pregnancy complications in women with a history of late fetal loss and placental infarction without thrombophilia: risk of recurrence and efficacy of pharmacological prophylactic interventions. A 10-year retrospective study

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**ABSTRACT**

**Purpose:** To evaluate the risk of recurrence of severe placenta-mediated pregnancy complications and compare the efficacy of two different anti-thrombotic regimens in women with a history of late fetal loss without thrombophilia.

**Patients and methods:** We performed a 10-year retrospective observational study (2008–2018) analyzing a cohort of 128 women who suffered from pregnancy fetal loss (>20 weeks of gestational age) with histological evidence of placental infarction. All the women tested negative for congenital and/or acquired thrombophilia. In their subsequent pregnancies, 55 received prophylaxis with acetylsalicylic acid (ASA) only and 73 received ASA plus low molecular weight heparin (LMWH).

**Results:** Overall, one-third of all pregnancies (31%) had adverse outcomes related to placental dysfunction: pre-term births (25% <37 weeks, 5.6% <34 weeks), newborns with birth weight <2500 g (17%), and newborns small for gestational age (5%). The prevalence of placental abruption, early and/or severe preeclampsia, and fetal loss >20 weeks were 6%, 5%, and 4% respectively. We found a risk reduction for combination therapy (ASA plus LMWH) compared with ASA alone for delivery <34 weeks (RR 0.11, 95% CI: 0.01–0.95 $p = 0.045$) and a trend for the prevention of early/severe preeclampsia (RR 0.14, 95% CI: 0.01–1.18, $p = 0.0715$), while no statistically significant difference was observed for composite outcomes (RR 0.51, 95%CI: 0.22–1.19, $p = 0.1242$). An absolute risk reduction of 5.31% was observed for the ASA plus LMWH group. Multivariate analysis confirmed a risk reduction for delivery <34 weeks (RR 0.32, 95% CI 0.16–0.96 $p = 0.041$).

**Conclusion:** In our study population, the risk of recurrence of placenta-mediated pregnancy complications is substantial, even in the absence of maternal thrombophilic conditions. A reduction of the risk of delivery <34 weeks was detected in the ASA plus LMWH group.

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## Introduction

Placenta-mediated complications (including early/severe preeclampsia, placental abruption, fetus small-for-gestational-age (SGA), and/or low birth weight) related to fetal loss represent an important health issue, with serious repercussions on women's health and on the unborn child. The recurrence risk in a patient with a history of placenta-mediated obstetrical complications is about 30–50% [1–4], thus, these patients require careful follow-up and effective interventions to prevent further obstetrical complications. The association between thrombophilia and fetal loss raised expectations about the potential clinical efficacy of anti-thrombotic prophylaxis in this setting, but limited evidence has been reported so far and no agreement among experts has been found about the optimal regimen. In particular, the role of this prophylactic treatment in patients without congenital and/or acquired thrombophilia is not clear.

Our study aimed to investigate the risk of recurrence of placenta-mediated complications in women

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with a history of fetal loss over 20th weeks in a previous pregnancy and without evidence of a congenital or acquired thrombophilic state. Furthermore, in the same group of patients, we investigated the efficacy of two prophylactic pharmacological regimens (ASA and LMWH + ASA) in preventing placenta-mediated complications and improving obstetrical outcomes in a subsequent pregnancy.

## Materials and methods

We performed an observational retrospective study analyzing women who delivered their first child between 2008 and 2018 at the Sant'Anna Hospital, Turin (Italy), a large maternity hospital with over 6,000 annual deliveries, recognized as a referral center for complicated pregnancies and premature newborns. Patients were identified and recruited using antenatal and obstetric databases. Case notes and laboratory results were reviewed by a team of physicians with maternal-fetal medicine expertise to select patients ($N = 128$) according to the following inclusion criteria:

1. Fetal loss at >20th weeks, associated with one or more of the following conditions: early-onset or severe preeclampsia, HELLP syndrome, placental abruption, and fetal growth restriction (FGR) [5,6]. According to NICE guidelines [7], severe preeclampsia was defined as a form of preeclampsia with severe hypertension that does not respond to treatment or is associated with ongoing or recurring symptoms (severe headaches, visual scotomas, nausea or vomiting, epigastric pain, oliguria) as well as progressive deterioration in laboratory blood tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal doppler findings. Early-onset preeclampsia was defined according to the cutoff of 34 weeks of gestational age [7].
2. Exclusion of other causes of fetal demise such as infections, malformations, cord abnormalities, chromosomal abnormalities, cervical incontinence;
3. Histological evidence of placental infarction [8];
4. No known congenital or acquired maternal thrombophilic state.

All women tested negative for both congenital (antithrombin deficiency, protein C and protein S deficiency, factor V R506Q polymorphism, factor II G20210A polymorphism) and acquired thrombophilia (lupus anticoagulant and anticardiolipin antibodies IgG and IgM, anti-beta 2 GP1 IgG and IgM, essential thrombocythemia). The tests were carried out after the index pregnancy diagnosis and repeated during the 1st trimester to screen for acquired thrombophilia.

At our institution, during the study timeframe, this subset of patients was treated either with low-dose Acetylsalicylic Acid (ASA) plus Low Molecular Weight Heparin (LMWH) ($n = 73$) or low-dose Acetylsalicylic Acid ($n = 55$) alone for the prevention of placenta-mediated complications. All patients received the anti-thrombotic treatment from the beginning of the subsequent pregnancy (positive pregnancy test) and was stopped at the 34$^{th}$ week of gestational age. The specific regimen was selected by the attending obstetrician on a case-by-case basis. In particular, 3 physicians took care of these patients within the high-risk pregnancy service of our hospital during the time period of the present study and prescribed all the anti-thrombotic treatments.

ASA was administered at the dose of 1 mg/kg/day and subcutaneous LMWH (enoxaparin sodium) at a prophylactic dose of 4,000 IU or 6,000 IU daily, according to patient weight (< or >90 kg). In our institute, this dosage of ASA was chosen because of the available evidence suggesting that 1–2 mg/kg results in a dose-dependent inhibition of thromboxane synthesis in platelets, without significantly affecting endothelial prostacyclin formation [9].

All women gave their consent to antithrombotic prophylaxis and for the use of clinical data. The Institutional Review Board approved the study (protocol n° 0108566) and results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [5]. All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki and following Good Clinical Practice rules.

All women underwent a placental biochemical function test early in the 2nd trimester, a serial biophysical assessment with ultrasound imaging including uterine and umbilical arteries Doppler at the 20$^{th}$ week, monthly biochemical test and clinical surveillance; increased surveillance was performed if fetal FGR was suspected.

All women were followed as outpatients throughout pregnancy to delivery and in case of complications, admitted to the hospital. For every pregnancy, we collected time and mode of delivery, birth weight, APGAR score, and diagnosis of preeclampsia, thrombosis, placental abruption, stillbirth, miscarriage, or fetal demise. The newborn weight percentile was reported according to the standard Italian birth weight

charts, adjusted for sex, parity, and gestational age [6]. SGA was defined as a weight below the 10th percentile. A plausible composite adverse outcome was conceived based on five clinically and equally meaningful components: prematurity <34 weeks, severe or early-onset preeclampsia, SGA <10th percentile, pregnancy loss >20 weeks, and placental abruption.

In all cases of fetal loss, a pathological examination of the placenta and fetus was performed.

The single-center follow-up helped reduce variability bias in the assistance provided during pregnancy and delivery. A bias in treatment starting time was excluded, given that all patients started treatment within the first trimester. Moreover, all patients assumed the therapy up to the endopoint of 34 weeks of gestational time, except in cases where delivery occurred before this cutoff.

The associations between the allocated treatment regimen (ASA alone vs ASA plus LMWH) and maternal age, BMI >30, and ethnic group were analyzed to exclude potential biases.

The statistical analysis was carried out on the study group as a whole and the ASA versus ASA + LMWH-treated patients. Continuous variables were analyzed with the Student's T-test. Differences in dichotomous outcomes between the two study groups were analyzed with the use of the chi-square test or Fisher's exact test when the anticipated cell frequencies were below five. We compared the proportion of patients experiencing one or more of the composite outcome events, using an unadjusted chi-square test of proportions. To determine the effect of key prognostic factors, a univariate analysis was performed and a multivariate logistic regression model was developed comparing outcomes as a whole and within the two groups. Descriptive data are presented as percentages or means, standard deviation (SD), and standard error of the mean (SEM), to facilitate the comparison. All statistical tests were two-sided and significance was set at $p$-value <0.05. Confidence intervals not including 1.00 were regarded as statistically significant.

## Results

Overall, a 94% live birth rate was observed among the subsequent pregnancies. About two-thirds (69%, 88/128) of them had an uneventful clinical course with the delivery of a healthy newborn, while 40 (31%) pregnancies had at least an adverse outcome related to placental dysfunction.

The two treatment groups did not differ in their clinical and sociodemographic features, except for a higher proportion of previous spontaneous abortions <12 weeks in the group treated with ASA + LMWH ($p = 0.02$) (Table 1).

### *Analysis of maternal/fetal outcomes according to treatment regimen*

A risk reduction in favor of combined prophylaxis was observed in terms of prematurity <34 weeks (RR 0.11, 95% CI: 0.01–0.95 $p = 0.0455$), while a trend was detected for early/severe preeclampsia (RR 0.14, 95% CI: 0.01–1.18 $p = 0.0715$). Mean birth weight and gestational age at delivery of live births were similar between the two groups. There was no difference according to all other fetal outcomes (Table 2). A multivariate logistic regression analysis partially confirmed the results of the univariate analysis. In particular, the risk reduction of prematurity <34 weeks remained significant after multivariate analysis (RR 0.32, 95% CI 0.16–0.96 $p = 0.041$). All premature births <34 weeks were C-sections for placenta-mediated complications (5 for early/severe preeclampsia, 2 for placental abruption).

No significant differences (RR 0.51, 95% CI: 0.22–1.19, $p = 0.12$) were observed considering a composite outcome including the five main adverse obstetric outcomes (prematurity <34 weeks, early/severe preeclampsia, SGA < 10th percentile, pregnancy loss >20 weeks, placental abruption). Finally, we observed a 5.31% (32.88% versus 38.18%) absolute risk reduction for complicated pregnancies (any complication) in favor of combined treatment, however, this result did

**Table 1.** Baseline characteristics of analyzed patients.

| | ASA + LMWH N. 73 | ASA N. 55 | $p$ |
|---|---|---|---|
| Maternal age | 33 (SD 5.29 SEM 0.62) | 33 (SD 4.71 SEM 0.63) | – |
| Pre-pregnancy BMI | 24.9 (SD 4.52 SEM 0.53) | 26 (SD 5.39 SEM 0.73) | – |
| Mean gestational age of previous maternal loss | 35 (SD 4.2 SEM 0.61) | 36 (SD 5.6 SEM 0.70) | – |
| BMI >30 % | 13 | 19 | 0.335 |
| Previous miscarriage <12 weeks (*N*) | 30 | 21 | 0.02 |
| Family history of thromboembolic events* | 10 | 6 | 0.63 |
| Current smoker (*N*) | 3 | 4 | – |
| Race/ethnic group (*N*) | White 71<br>Black African 2 | White 53<br>Black African 2 | – |

*Only first degree parents were considered.

**Table 2.** Analysis of maternal and fetal outcomes in the whole series and according to treatment.

| Maternal outcome | Total *N.* 128 | *N.* % | ASA + LMWH *N.* 73 | *N.* % | ASA N. 55 | *N.* % | RR | 95%CI | P |
|---|---|---|---|---|---|---|---|---|---|
| Delivery <37 ° weeks | 32 | 25 | 16 | 22 | 16 | 29 | 0.85 | 0.46–1.56 | 0.615 |
| <34 ° weeks | 7 | 5 | 1 | 1.3 | 6 | 11 | 0.11 | 0.01–0.95 | 0.045 |
| Early/severe preeclampsia | 6 | 5 | 1 | 1.3 | 5 | 10 | 0.14 | 0.01–1.18 | 0.071 |
| Placental abruption | 8 | 6 | 3 | 4 | 5 | 10 | 0.42 | 0.10–1.70 | 0.229 |
| Cesarean Section | 80 | 62 | 44 | 60 | 36 | 65 | – | – | – |
| Pregnancy-related thrombosis | 0 | 0 | 0 | – | 0 | – | – | – | – |
| **Fetal outcome** | | | | | | | | | |
| Weight <2500 g. | 23 | 18 | 12 | 16 | 11 | 20 | 0.77 | 0.37–1.62 | 0.504 |
| SGA <10° percentile | 6 | 5 | 4 | 6 | 2 | 4 | 1.42 | 0.27–7.49 | 0.676 |
| SGA <5° percentile | 5 | 4 | 4 | 6 | 1 | 2 | 2.85 | 0.32–24.8 | 0.341 |
| Miscarriages <20 weeks | 3 | 2 | 0 | 0 | 3 | 5 | 0.10 | 0.00–2.05 | 0.138 |
| Fetal losses >20 weeks | 8 | 6 | 3 | 4 | 5 | 10 | 0.45 | 0.11–1.81 | 0.262 |
| Mean birth weight g (SD) | 2834 (525) | | 2854 (495) | | 2813 (692) | | – | | 0.63 |
| Weeks at Delivery (SD) | 37.1 (1.88) | | 37.3 (1.56) | | 37.1 (2.35) | | – | | 0.58 |

not reach statistical significance (95% CI: −11.46% to 22.07%, $p = 0.21$).

## Discussion

Successful pregnancy outcomes depend on the efficiency of placental circulation. Placental vascular thrombosis and abnormal placenta development are at least partly responsible for placenta-mediated pregnancy complications and the risk of recurrence is substantial. Women with prior severe preeclampsia have a 25% to 65% risk of recurrent preeclampsia, a 3% risk of placental abruption, and a 10% risk of SGA <10th percentile [1–4,10].

Our study focused on a very specific subset of patients with common clinico-pathological features: obstetric history of fetal loss >20 weeks, histologically proven placental infarction and no known predisposing factors for the development of thrombosis. However, it should be noted that this latter finding should not lead physicians to overlook the increased risk of recurrence of placenta-mediated complications in subsequent pregnancies as shown by our data. A detailed obstetric history provides a high predictive value of future complications and is a simple and useful tool for clinicians. Unfortunately, although multiple potential antithrombotic prophylactic treatments are currently available, their efficacy seems to be limited and the choice of the optimal regimen for these women has not yet been adequately addressed and it is largely empirical.

Previous data shows that low dose-aspirin administered from the 1st trimester is associated with small relative risk reductions in patients with prior preeclampsia, its efficacy being higher in those women who experienced early preeclampsia and FGR [10,11].

LMWH appears to be another promising preventive therapy for these serious pregnancy complications and it may share with ASA some additional mechanisms of action unrelated to the anticoagulant activity, including modulation of trophoblast proliferation and invasiveness, pro-angiogenic effects [12,13] and suppression of complement pathway activation [14,15].

Several studies have tried to demonstrate the usefulness of anticoagulant prophylaxis to prevent adverse obstetrical outcomes, but these results are heterogeneous and based on limited evidence. A meta-analysis conducted on the currently available main randomized controlled trials (RCT) found that prophylactic LMWH might be useful only in a subgroup of patients with prior late and severe placenta-mediated pregnancy complications [15,16].

A possible benefit of the combination of ASA plus LMWH is reported: some recently published RCT and systematic reviews suggest either a significant reduction of early-onset recurrent hypertensive disorders in thrombophilic women or a trend toward efficacy [17,18]. It is plausible that the combination of ASA plus LMWH may be advantageous in patients with more severe placenta-mediated pregnancy complications, but the data is still heterogeneous and conflicting [19,20].

Our study observed an overall 31% risk of placenta-mediated pregnancy complications in this subset of patients despite a live birth rate of over 90%. Given data from previously published studies, it was no surprise that the preterm delivery of SGA infants is an important predictor of the subsequent risk of stillbirth, preeclampsia, and preterm delivery [3]. In particular, we found a relatively high number of SGA in this cohort of patients, probably due to the high intrinsic risk of these pregnancies, despite not showing evidence of the most common acquired and congenital thrombophilic alterations.

The group of patients treated with ASA plus LMWH showed a significant advantage only in terms of the prevention of preterm delivery <34 week and

this finding was also confirmed by multivariate analysis. A trend for the prevention of pre-eclampsia development was detected in the univariate analysis, while no differences were observed in terms of adverse fetal outcomes. Interestingly, all deliveries <34 week were by Cesarean section because of placenta-mediated complications (early/severepreeclampsia or placental abruption) supporting a preventive role for this event of combination therapy with ASA plus LMWH.

Our study showed a marginal, nonsignificant advantage for the combined treatment in terms of complicated pregnancies (any complication), with an absolute risk reduction of 5.31%.

The main strength of our study is that we selected a homogeneous, very high-risk group of non-thrombophilic women with histologically confirmed placenta-mediated pregnancy complications. This is relevant because the results of other studies derived from the analysis of heterogeneous groups of women, including both thrombophilic and non-thrombophilic patients, with prior placenta-mediated pregnancy complications of varying severity [21–23]. Finally, the same expert pathologist performed all the fetal autopsies and histological examinations of the placenta samples (GB). The main limitation of the present study is intrinsic to its retrospective non-randomized design leading to potential biases in terms of treatment allocation. Concerning this issue, we observed a higher rate of abortions at <12 weeks of gestational age in the combined treatment group, a characteristic which could potentially have affected treatment selection. Despite these limitations, the study addresses a relevant real-world issue and tackles the unmet clinical need of establishing effective preventive treatments for this rare population.

## Conclusions

Close surveillance is mandatory in this specific group of patients since the risk of recurrence and adverse obstetric outcomes remains higher during subsequent pregnancies. The combination of ASA + LMWH compared with ASA alone seems to provide a benefit in terms of risk reduction of prematurity <34 weeks. However, these results should be interpreted with caution due to the study design and the low number of analyzed events. Despite the rarity of the studied population, it would be highly desirable to obtain data from prospective studies to clarify the best therapeutic strategy.

## Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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