

N. SANTOS¹, Â. GASPAR¹, S. LIVRAMENTO², G. SAMPAIO¹, M. MORAIS-ALMEIDA¹

Aspirin desensitization in a woman with inherited thrombophilia and recurrent miscarriage

¹Immunoallergy Department, CUF Descobertas Hospital, Lisbon, Portugal - E-mail: angela.gaspar@sapo.pt

²Medicine Department, CUF Descobertas Hospital, Lisbon, Portugal

KEY WORDS

Acetylsalicylic acid; aspirin; desensitization; inherited thrombophilia; recurrent pregnancy loss

Corresponding author

Dr. Ângela Gaspar
Immunoallergy Department,
CUF Descobertas Hospital
Rua Mário Botas,
1998-018 Lisboa, Portugal
Tel. +351 917057233
Fax +351 210025220
E-mail: angela.gaspar@sapo.pt

SUMMARY

Women with inherited thrombophilia and recurrent miscarriage might benefit from preconceptual antiaggregation with low-dose acetylsalicylic acid (ASA), but concerns about severe adverse reactions may prevent physicians from performing this treatment in patients with ASA hypersensitivity. We report the first known case of ASA desensitization in a 41-year-old woman with inherited thrombophilia, who had homozygosity (4G/4G polymorphism) of the plasminogen activator inhibitor-1 (PAI-1) gene and first trimester recurrent miscarriage, and had previously presented with anaphylaxis to ASA. Desensitization was completed despite one self-limited adverse reaction, and the patient has maintained a daily ASA intake of 100mg with good tolerance.

Recurrent miscarriage, defined as three or more first trimester pregnancy losses, is devastating for women and their families. Women with inherited thrombophilia and recurrent miscarriage might benefit from preconceptual antiaggregation with low-dose acetylsalicylic acid (ASA), but concerns about severe adverse reactions may prevent physicians from performing this treatment in patients with ASA hypersensitivity (1-3). Desensitization to ASA, commonly known as aspirin, is an essential procedure in patients with ASA hypersensitivity who need chronic treatment with this drug. It was first described in 1922 by Widal et al. (4) and is most frequently performed for the treatment and prophylaxis of cardiovascular diseases and in aspirin-exacerbated respiratory disease (5-9). It has also been described before or during pregnancy in women with antiphospholipid syndrome (10), but to our knowledge it has not been previously held in other thrombotic diseases.

We present the case of a 41-year-old woman with three consecutive miscarriages before 8 weeks of pregnancy, in whom the study for thrombophilia revealed an inherited thrombophilia, with exclusion of other causes including antiphospholipid syndrome. Genotyping analysis showed homozygosity (4G/4G polymorphism) for the plasminogen activator inhibitor-1 (PAI-1), which results in elevated PAI-1 concentrations and decreased fibrinolysis, and is associated with a greater risk of thromboembolic events and recurrent miscarriages (11). She has an intermittent allergic rhinitis with sensitization to grass pollens. Six years prior, she experienced an anaphylactic reaction with generalized urticaria and respiratory distress immediately on taking a non-specified dose of ASA. Afterward she had a cutaneous reaction with generalized urticaria within 30 minutes of intake of ibuprofen 200 mg. Both reactions required hospital attendance, with resolution after being medicated with anti-histamine and corticosteroid. She

tolerates paracetamol and preferential COX-2 inhibitors non-steroidal anti-inflammatory drugs, nimesulide and meloxicam. As ASA in low-dose is the best therapeutic option for antiaggregation during pregnancy (1-3, 10), the patient was referred to our Immunoallergy Department for ASA desensitization before the next pregnancy.

In May 2011 we obtained the patient's written informed consent, and the ASA desensitization was carried out in hospital setting using increasing oral doses of ASA, with a starting dose of 0.1mg, following the protocol presented in table 1, modified from those of Rossini et al. (8) and Wong et al. (5). The oral desensitization was performed with 8 sequential doses of ASA (0.1, 1, 5, 10, 20, 40, 75 and 100 mg); doses were increased every 30 minutes, with a 120 minute interval before the last dose. Patient's blood pressure, cardiac rate and oxygen saturation were regularly measured, and cutaneous, naso-ocular, and pulmonary reactions were monitored closely, with spirometric surveillance before initiation, after each step and before hospital discharge.

Within 15 minutes of 10 mg ASA oral administration, the patient reported rhinitis and a 10% fall from baseline in the forced expiratory volume in one second (FEV1) from 3.14 to 2.83 liters, and a 17.4% fall in the maximum midexpiratory flow (MMEF75/25) from 3.21 to 2.65 liters, with spontaneous improvement and clinical and spirometric resolution in 30 minutes, thus confirming ASA hypersensitivity and delaying the next administration to 90 minutes instead of 30 minutes later. The patient completed the desensitization protocol in 6 hours with a total cumulative dose of 251.1 mg of ASA and was discharged from the hospital after 2 hours' surveillance. She has since maintained a daily ASA intake of 100mg in a single dose with good tolerance.

To our knowledge this is the first reported case of an ASA desensitization performed in a women with an in-

herited thrombophilia, in this case a homozygosity of the PAI-1 gene. It is estimated that 5% of women of reproductive age have two or more recurrent pregnancy losses and around 1% have three or more losses. Acquired thrombophilia, as antiphospholipid syndrome, as well as inherited thrombophilia, may benefit from antiaggregation with low-dose ASA therapy, alone or in association with low molecular weight heparin (1-3, 12), meaning inherited thrombophilia with recurrent miscarriage could be included in the indications for ASA desensitization in woman with ASA hypersensitivity.

References

1. Robertson L, Wu O, Langhorne P, et al. Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2006; 132: 171-96.
2. Greer IA. Antithrombotic treatment for recurrent pregnancy loss? *J Thromb Haemost* 2011; 9 (Suppl.1): 302-5.
3. Kosar A, Kasapoglu B, Kalyoncu S, Turan H, Balcik OS, Gümüş EI. Treatment of adverse perinatal outcome in inherited thrombophilias: a clinical study. *Blood Coagul Fibrinolysis* 2011; 22: 14-8.
4. Widal MF, Abrami P, Lenmoyez J. Anaphylaxie et idiosyncrasie. *Presse Med* 1922; 30: 189-92.
5. Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000; 105: 997-1001.
6. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 2006; 6: 476-81.
7. Lee JY, Simon RA, Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2007; 119: 157-64.
8. Rossini R, Angiolillo DJ, Musumeci G, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol* 2008; 101: 786-9.
9. Cernadas JR, Brockow K, Romano A, et al. European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy* 2010; 65: 1357-66.
10. Alijotas-Reig J, San Miguel-Moncín M, Cisteró-Bahíma A. Aspirin desensitization in the treatment of antiphospholipid syndrome during pregnancy in ASA-sensitive patients. *Am J Reprod Immunol* 2006; 55: 45-50.
11. Buchholz T, Lohse P, Rogenhofer N, Kosian E, Pihusch R, Thaler CJ. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. *Hum Reprod* 2003; 18: 2473-7.
12. Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol* 2009; 36: 279-87.

Table 1 - ASA desensitization protocol [modified from Rossini et al. (8) and Wong et al. (5)]

Time (min)	Dose (mg)	Cumulative dose (mg)
0	0.1	0.1
30	1.0	1.1
60	5.0	6.1
90	10.0	16.1
*180	20.0	36.1
210	40.0	76.1
240	75.0	151.1
360	100.0	251.1

* Time adjustment due to previous reaction