CASE REPORT

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Acetylsalicylic acid desensitization in an allergic pregnant woman post-vascular scaffolds implantation

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Key words

Acetylsalicylic acid; desensitization; hypersensitivity drug reactions; NSAID hypersensitivity; pregnancy.

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Summary

The use of acetylsalicylic acid (ASA) desensitization for patients with coronary artery disease (CAD) is growing, but no data are available on desensitization protocol in patients with ASA sensitivity and CAD during pregnancy. This case report shows that ASA desensitization protocol during pregnancy could be safe and effective in a tertiary center with a multidisciplinary team.

Impact statement

ASA desensitization protocol during pregnancy could be safe and effective in a tertiary center with a multidisciplinary team.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA), are associated with adverse effects, ranging from mild gastritis to life-threatening reactions. The overall prevalence of hypersensitivity reactions ranges from 0.6-6%, but no prevalence data are available in pregnant women (1).

The mechanism of action of NSAIDs is the inhibition of the cyclooxygenase (COX) enzymes. There are two main COX isoforms, COX-1 (which is expressed constitutively in all human cell types and is involved in protective physiologic functions) and COX-2 (which is an inducible enzyme expressed in many inflammatory cells in presence of appropriate stimuli) (2).

ASA, a strong COX-1 inhibitor preventing platelet aggregation, is a key-treatment for patients with coronary artery disease (CAD) and is also a cornerstone component of dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ receptor blocker. However, hypersensitivity or intolerance may restrict its use (3).

In literature only four cases on ASA desensitization during pregnancy have been published, especially in women diagnosed with antiphospholipid syndrome (4).

Since there are no commercially available tests to detect NSAIDs hypersensitivity, a diagnostic strategy successfully used for decades is to challenge patients with past mild reactions to NSAIDs. However, ASA desensitization protocol is mandatory in case of positive challenge, or for safety reasons in history of severe reaction, or unstable pathology with compelling need for

aspirin (5). Increasing doses of ASA under medical supervision are subsequently administered to the patient inducing a state of temporary tolerance (6). After a successful ASA-desensitization, the patient, in order to maintain tolerance, must assume the drug daily (4).

In patient suffering from an established cardiovascular disease or a high-risk patient, a daily therapy with ASA can reduce the risk of subsequent adverse cardiovascular events such as myocardial infarction, stroke, and vascular death (2). For this reason, ASA sensitivity is particularly problematic for individuals who need an urgent or emergency neurologic or cardiac procedure, such as artery stenting (coronary, carotid, or other) or following the diagnosis of an ischemic neurologic event.

Case presentation

We describe a case of a 42-year-old pregnant woman, with a past medical history of arterial hypertension, type 2 diabetes mellitus, dyslipidemia and overweight, affected by CAD, with prior percutaneous coronary intervention (PCI) with two overlapping bio-resorbable vascular scaffolds (Absorb) for unstable angina. After PCI she started DAPT with Clopidogrel and Indobufen.

She was referred to our tertiary center during the fifth month of pregnancy for an allergological evaluation. She was no longer in DAPT because Indobufen was interrupted by her cardiologist when her pregnancy became known (9 months after PCI). Then, a multidisciplinary team of obstetricians and experts of the Thrombosis and Coagulation Department recommended to restart DAPT with Clopidogrel and ASA as the best choice, considering the high risk of late stent thrombosis related to stent type (Absorb), number and procedural techniques (two stents in overlap), diabetes and pregnancy. Unfortunately, the patient had a positive history of hypersensitive reaction to ASA: some years before she had experienced an adverse reaction consisting in labial and periocular angioedema immediately (about 10 minutes) after ASA intake. Nevertheless, she tolerated other NSAID such as Indobufen, Ibuprofene and Ketoprofen. In this setting it was conceivable assuming patient reaction as a single NSAID-induced urticaria/angioedema (SNIUA) (7). Even if desensitization procedures are widely used in cardiological clinical practice, they are not recommended during pregnancy for the risk of anaphylactic reaction that could lead to fetal and maternal damages. However, a recent Food & Drug Administration (FDA) warning reported an increased rate of major adverse cardiac events observed in patients with bio-absorbable device (8).

After a consultation with a multidisciplinary team (anesthesiologists, obstetricians, cardiologists and hematologist), considering the relative low risk of an anaphylactic reaction *versus* the high risk of a stent thrombosis (11%), our Outpatients Allergy Department decided to perform an ASA desensitization treatment, followed by constant administration of the same drug at a disaggregating dose (100 mg/daily) (8, 9).

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. The patient signed an informed consent and started a desensitization protocol in an intensive care unit of the Obstetrical Department with maternal and, if necessary, fetal monitoring.

The first day ten increasing doses of acetylsalicylic acid at 30-minute intervals were orally given to the patient, until the cumulative dose of 100.1 mg was reached, using Cortellini *et al.* desensitization protocol (**table I**) (5). The following day, the full dose of 100 mg was administered successfully and from that day, the patient assumed the same dose every day. No reaction was observed

Table I *- ASA desensitization protocol by Cortellini et al. [8].*

Number of doses (every 20 minutes)	mL of solution (10 mg/mL)	Dose of ASA (mg)	Cumulative dose (mg)
1	0 (placebo)	--	--
2	0.01	0.1	0.1
3	0.10	1	1.1
4	0.20	2	3.1
5	0.30	3	6.1
6	0.40	4	10.1
7	0.50	5	15.1
8	1.00	10	25.1
9	1.50	15	40.1
10	2.50	25	65.1
11	3.50	35	100.1

during the desensitization procedure and the following days. No antihistamine premedication was administered due to the possibility to mask any eventual muco-cutaneous reaction, a possible red flag of a more severe reaction.
The patient underwent, as planned, cesarean section scheduled on the 34th week, giving birth to a healthy child. DAPT was interrupted, stopping the administration of clopidogrel alone, from 5 days before to 1 day after the delivery.
Mother and newborn were both asymptomatic and in good general condition at a six-month follow-up after delivery.

Discussion and conclusions

Since the worldwide increasing use, NSAIDs are the most important drug involved in hypersensitivity reactions. According to the nomenclature of the EAACI/AAAAI task force, drug hypersensitivity reactions are classified as allergic and non-allergic (6).
ASA-hypersensitivity constitutes a serious problem for subjects with NSAID sensitivity and concomitant CAD, so ASA desensitization has to be considered, given the excellent clinical efficacy, low risk profile, and cost-effectiveness (10).
Moreover, during pregnancy, low-dose of ASA is indicated for prevention of preeclampsia, fetal growth restriction, stillbirth or obstetric complications related to antiphospholipid syndrome (9).
Based on the patient's clinical history and presentation (an immediate reaction after ASA intake), after a multidisciplinary evaluation, considering the greater risk of stent thrombosis compared to that of ASA reaction, we decided to use a desensitization protocol as the best approach in a pregnant patient with previous allergic reactions to ASA. This because ASA in association with clopidogrel is up to now considered the real effective therapy in patients affected by CAD with medicated stent (11).
Since an ASA challenge was not performed before pregnancy, desensitization has been carried out in a multidisciplinary setting with access to resuscitation facilities and an intensive care unit for maternal and fetal monitoring (4).
Even if desensitization procedures could be at risk during pregnancy, this case shows that, in a patient with a history of mild reaction to ASA, a desensitization protocol during pregnancy may be safe and effective in a tertiary center with a multidisciplinary team, thus making it a valuable option, when the drug is mandatory for the patient. Nonetheless, given the lack of international standardization protocols and limited published data available, more studies are necessary to establish the risks and benefits for ASA-desensitization protocols in ASA-sensitive pregnant women.

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Contributions

VP, FR: resources. ACG, AS: writing – original draft, data curation. All authors: writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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