Use of ticagrelor in human pregnancy, the first experience

TITLE OF CASE

Use of ticagrelor in human pregnancy, the first experience

SUMMARY

Ticagrelor was daily administered throughout all pregnancy to a 37-year old pregnant woman until 36 weeks of gestation. The patient, with Behçet disease, suffered from a non-ST elevation myocardial infarction 4 months before conception, possibly related to hypertension and tobacco abuse. Pregnancy and postpartum period were uneventful. She delivered a healthy but small-for-gestational age term neonate.

BACKGROUND

We report the first case of use of ticagrelor during pregnancy. Ticagrelor is a new class of antiplatelet agent used as secondary prevention in combination with acetylsalicylic acid after an acute coronary syndrome. Class C was assigned to this new drug by the US Food and Drug administration. Data of use in human pregnancy are inexistent.

CASE PRESENTATION

A 37-year old woman with Behçet disease suffered from a non-ST elevation myocardial infarction (NSTEMI). Mild stenosis of the left anterior descending (LAD) coronary artery was treated with implantation of a drug-eluting stent through percutaneous coronary intervention (PCI). Following the hospital guidelines ticagrelor 90mg 2x/d for 1 year in combination with acetylsalicylic acid 80mg 1x/d (life time) was initiated for secondary prevention as was atorvastatin 40 mg daily.

Other cardiac risk factors included hypertension and smoking (30cigarettes per day). Antihypertensive treatment included perindropil 5mg and bisprolol 5mg daily. Behçet disease was at the same time treated with cyclosporine 50mg (b.i.d.), prednisolone 8mg and colchicine 1mg daily. Her obstetric history included caesarean section for breech position and a subsequent uneventful term vaginal.

The patient was counseled not to become pregnant after this recent acute coronary syndrome and daily treatment with cyclosporine, however she stopped her oral contraception and presented with a spontaneous singleton pregnancy 4 months after the NSTEMI.

INVESTIGATIONS

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DIFFERENTIAL DIAGNOSIS

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TREATMENT

At the first prenatal visit at 6 weeks of gestation cyclosporine, atorvastatin and colchicine were discontinued. Perindopril was replaced by amlodipine 5mg daily and after multidisciplinary counselling between obstetricians, cardiologists and neonatologists, it was advised to continue the treatment with ticagrelor for 8 months, until 7 days before a planned delivery.

Acetylsalicylic acid 80mg 1x/d, prednisolone 8mg 1x/d and bisoprolol 5mg 1x/d were continued throughout the whole pregnancy.

Regular prenatal follow-up was provided (1 visit/3weeks) with Doppler examination of the uterine artery at 12, 18 and 22 weeks of gestation.

Cardiac check-ups with clinical exam, electrocardiography and cardiac ultrasound were planned. Ophtalmologic exam was conducted at 28 weeks of gestation.

OUTCOME AND FOLLOW-UP

The pregnancy was uneventful. The patient did not suffer from flare-ups of Behçet's disease during pregnancy. Prenatal ultrasound exams, cardiac and ophthalmologic check-ups did not show any abnormalities.

Ticagrelor was stopped at 36 weeks of gestation because the patient complained of episodes of painful contractions, endovaginal measurement of cervical length was 10mm. Actual labour did not start and induction was performed at 38 weeks with intracervical dinoproston gel (Prepidil®, Ferring, Belgium). During labour amniotomy was performed and intravenous oxytocin was given according to local protocol. The patient received epidural anaesthesia (puncture with 17 Gauge Tuohy needle, epidural catheter and continuous administration of a mixture of hyperbaric bupivacaine and sufentanil). She delivered without any problems of a healthy baby boy of 2645g (5 th percentile for our local population), Apgar scores 8/9/10 after 1, 5 and 10 minutes respectively, umbilical artery pH 7.24. 5 IU oxytocin intravenously were given after delivery, as routinely in our hospital.

No significant events occurred in the postpartum period. At this moment the patient gives breast feeding. Cyclosporine, colchicine and atorvastatin will be administered again after the lactation period.

Histopathologic examination of the placenta demonstrated no specific lesions, but did show iron-loaded macrophages in the deciduas, suggesting antenatal bleeding, although this was never noted clinically.

DISCUSSION

To our knowledge this is the first report on the use of ticagrelor in pregnancy. Ticagrelor is a new and powerful antiplatelet agent. Ticagrelor is a nucleoside analogue and reversibly blocks the P2Y12 receptor(1). P2Y12 inhibitors increase the risk of bleeding. Potential complications in pregnancy could include: antenatal vaginal bleeding, placental abruption, postpartum hemorrhage, placental transmission resulting in fetal/ neonatal bleeding and eventual problems due to hemorrhage during neuraxial anaesthesia . Clopidogrel is the P2Y12R antagonist that is more widely used (2) . Several reports on the use of clopidogrel in pregnancy have been published, recently these have been reviewed. Based on the limited available data, clopidogrel in pregnancy has not been linked to maternal or fetal/ neonatal complications.

The association of ticagrelor with acetylsalicylic acid was superior in prevention of a new trombo-embolic event after an acute coronary syndrome, compared to the association of clopidogrel and acetylsalicylic acid (3). The advised period of administration is 12 months. This new drug is a class C drug in pregnancy because no controlled data of use in human pregnancy exist and animal studies showed fetal mortality and/or abnormalities at doses greater than maximum administered in humans. In our case a multidisciplinary board decided that the benefits of administration of ticagrelor during this pregnancy in this patient, with multiple cardiac risk factors, outweighed the possible risks. If used in pregnancy, we considered to stop ticagrelor 7 days before planned delivery due to known time for resumption of normal coagulation.

The limited fetal growth in this case can be linked to several factors including the use or ticagrelor and/or the patient's vascular status and the use of polymedication (especially bisoprolol). Hypertension and smoking are important confounding factors as cause of the growth restriction. It is possible that some subclinical bleeding, resulting in the iron-loaded decidual macrophages is related to the use of either acetylsalicylic acid or ticagrelor.

LEARNING POINTS/TAKE HOME MESSAGES

- Ticagrelor is a new and effective drug in secondary prevention of trombo-embolic event after an acute coronary syndrome
- This is the the first reported case of ticagrelor in human pregnancy
- A small-for-gestational age fetus and subclinical decidual hemorrhage were noted

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FIGURE/VIDEO CAPTIONS

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