JOURNAL OF DRUG ASSESSMENT
2021, VOL. 10, NO. 1, 7–9
https://doi.org/10.1080/21556660.2020.1847926
Article 0017.R1/1847926

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CASE REPORT

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Intravitreal vascular endothelial growth factor (VEGF) inhibitor injection in patient during pregnancy

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ABSTRACT

Purpose: To report the clinical course of a woman treated with intravitreal bevacizumab during pregnancy.

Case report: A 27-year-old female with poorly controlled diabetes and a history of two previous miscarriage was referred to our hospital with sudden deterioration in visual acuity (VA) in her right eye. Ocular findings revealed severe Proliferative Diabetic Retinopathy (PDR) complicated with preretinal hemorrhages in her right eye, and after maximal Panretinal Photocoagulation (PRP) bilaterally, she was treated with intravitreal injection of bevacizumab (IVB) into the right eye. Twenty four hours after the bevacizumab injection, she reported vaginal bleeding, and ultrasound confirmed a 12-week pregnancy of which the patient was unaware. The patient suffered from pregnancy loss.

Conclusion: Use of intravitreal anti-VEGF by pregnant woman may only be justified if the potential benefit outweighs the potential risk to the fetus and only if clearly needed. Intravitreal bevacizumab during pregnancy in women with a history of miscarriage should be used with caution.

ARTICLE HISTORY
Received 25 May 2020
Accepted 5 November 2020

KEYWORDS
Intravitreal bevacizumab; diabetic retinopathy pregnancy; complication; miscarriage

Introduction

Intravitreal injection of the anti-vascular endothelial growth factor (anti-VEGF) agents is currently the first-line treatment in exudative age-related macular degeneration (AMD)[1]. It is also efficacious in many ocular diseases such as diabetic retinopathy, retinal vein occlusion, and choroidal neovascularization by other causes like high myopia[2], and uveitis-associated cystoid macular edema[1].

Therefore, younger patients including women of childbearing age and pregnancy receive intravitreal treatment more frequently. Pregnancy testing is not recommended for women before injection.

Effects of intravitreal injection of bevacizumab have been demonstrated on the non-injected fellow eye. It may cross into systemic circulation and enter the fellow[2]. Although no short-term systemic complications following intravitreal anti-VEGF injection for Retinopathy of prematurity (ROP) have been reported, the long-term systemic adverse effects on premature babies are unknown[1].

Intravitreal bevacizumab is injected at a much lower concentration within the eye, and the systemic exposure of IVB is much lower than the systemic use of intravenous bevacizumab. We report the clinical course of pregnancy in a woman treated with a single intravitreal injection of bevacizumab during the first trimester of pregnancy.

Case report

Around September 2016, a 27-year-old female patient began noticing decreased visual acuity (VA) in both eyes but failed to seek treatment. On 21 April 2017, she noticed a sudden deterioration in VA in her right eye. She was diagnosed with type 1 diabetes at the age of 10 when insulin therapy was started. However, regular follow-up visits were not maintained, and her diabetes was not controlled well. Previously two pregnancies ended in a miscarriage in the 9th and 12th week of pregnancy at the age of 23 and 25. She was obese, with the height of 160 cm and the weight of 96 kg.

The patient's ocular findings on initial examination were as follows: VA: right eye = 20/200; left eye = 20/100; intraocular pressure: right eye = 14 mm Hg; left eye = 16 mm Hg. Examination of the anterior eye segment showed neovascularization of iris in the right eye, and examination of the optic media showed mild bilateral cataracts. Funduscopy showed PDR in both eyes. It also demonstrated extensive fundal hemorrhages and deposit of hard exudates in the central fovea of the right eye. Extensive preretinal hemorrhages and areas of nonperfused retina were also observed in the right eye. The left eye showed extensive nonperfused areas of the retina with neovascularization. After maximal PRP bilaterally, she was treated with 1.25 mg/0.05 mL intravitreal bevacizumab injection into the right eye. Twenty four hours after the bevacizumab injection, she

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reported vaginal bleeding, and ultrasound confirmed a 12-week pregnancy of which the patient was unaware. The patient suffered from pregnancy loss. Her subsequent pregnancy was complicated by hypertension, and fetal death occurred at 24 weeks gestation. The approval of our institution (Isfahan university of medical sciences) was obtained with ethical committee number: IR.MUI.MED.REC.1399.365 approval date: 2020-08-03.

Discussion

Bevacizumab (Avastin; Genentech, South San Francisco, CA), a full-length humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), was approved by the U.S. Food and Drug Administration as a systemic treatment for metastatic colon or rectum carcinoma; unresectable, locally advanced, recurrent or metastatic nonsquamous non-small-cell lung cancer; glioblastoma; metastatic breast cancer; and metastatic renal cell carcinoma[1].

Adverse effects such as gastrointestinal perforation, impaired wound healing, hemorrhage in multiple organ systems, gastrointestinal fistula formation, arterial thromboembolic events, and hypertension use were reported in systemic administration[1].

The use of anti-VEGF agents during pregnancy and their safety remain questionable, since the antiangiogenic effect may have harmful effects on the placenta and developing fetus, especially in the early stages of pregnancy.

The use of bevacizumab during pregnancy (through transplacental transmission from mother to baby) may have the potential to cause harm to the baby.

There are no human studies on pregnant women to evaluate the safety of bevacizumab. Incorporation of Fc region in full-length bevacizumab antibody and binding with IgG may cross the placenta[2].

Bevacizumab has been demonstrated to be embryotoxic, and teratogenic in rabbits following intravenous administration. Additionally, it results in reduction in the fetal and maternal weight, it increases the number of resorbed fetuses, and increases the incidence of fetal skeletal abnormalities[3].

Furthermore, it is important to emphasize that spontaneous abortion is a surprisingly common occurrence. Ten to twenty percent of clinically recognized pregnancies end in miscarriage and 30 to 40 percent of all conceptions end in miscarriage[4].

Polizzi et al.[5] and Sarmad and Lip[6] in their studies have provided promising information on the fetal and maternal security profile of intravitreal hostile to VEGF agents in pregnant patients. There have been 4 described cases of abortion following IVB treatment[2,7,8].

Petrou et al.[7] described spontaneous miscarriage 7 and 10 days following administration of IVB at approximately 4 and 3 weeks of gestation. Spontaneous abortions occurred after a short time following intravitreal injection, and potential risk factors for miscarriage were lacking in these cases; therefore, relationship of intravitreal bevacizumab to increased risk of early loss of pregnancy is possible. However, since the baseline rate of miscarriage is high, it is unclear whether these 2 events were directly associated with IVB.

GóMez Ledesma et al.[8] described spontaneous abortion 7 weeks following single IVB in a 41-old-woman.

Spontaneous abortion rate increases remarkably after 40 years, reaching 41%[9].

Miscarriage rates more substantially increase after the age of 35, and it was impossible to determine the exact time of IVB use before or after beginning of pregnancy in this case. Therefore, it remains difficult to clearly establish a correlation between miscarriage and anti-VEGF.

We reported[2] a case of spontaneous abortion after a single IVB in a 29-year-old woman. The miscarriage occurred about 18 h after the injection. Whether these reported abortions are IVB related or due primarily to a higher baseline rate of fetal loss at an advanced maternal age is uncertain[8].

In 3 patients, a short period between the intravitreal injection and spontaneous abortions as well as absence of risk factors for a pregnancy loss propose an etiological correlation between bevacizumab injection and early loss of pregnancy.

In our case, it is more difficult to establish a correlation between miscarriage and anti- VEGF, since the patient has a history of two miscarriage and her subsequent pregnancy complicated by intrauterine fetal death by hypertension.

At present, anti-VEGFs have been used only in case reports or small case series during pregnancy. There are no prospective studies evaluating the effects of intravitreal anti-VEGF in pregnant women. Probably, information on human gestational drug exposure will not be derived from observational studies not controlled clinical trials. Some patients develop a panic attack just before or during the injection and blood pressure or heart rate may become problematic. Hence injecting potentially pregnant women should be reserved to: (1) pregnancy test negative (2) check vital sign before the injection (3) monitor the vital sign during the injection (4) assess the anxiety level vis-a-vis fears of injection (5) decrease the dose of the injection for several reasons FIRST the regular dose causes ocular hypertension and ocular pain SECOND the regular dose is 5 times what is needed THIRD less dose in the eye the lower the level in body FOURTH the lower dose cause less reflux or leak and less entry into the systemic circulation

In conclusion, intravitreal anti- VEGF can be used during pregnancy if the clinical benefit to the woman justifies the potential risk to the fetus, and checking the pregnancy status before injection is necessary and caution should be taken when anti-VEGF agents are used during pregnancy in women with a history of miscarriage.

Transparency

Declaration of funding

There was no funding received in the preparation of this article.

Declaration of financial/other relationships

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication. Authors do not have any financial interest in any products mentioned in this article. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

None stated.

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