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SHORT REPORT

Intravitreal vascular endothelial growth factor (VEGF) inhibitor injection in unrecognised early pregnancy

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Summary The use of intravitreal vascular endothelial growth factor (VEGF) inhibitor medications has widened considerably to include indications affecting females of reproductive age. Our patient was inadvertently exposed to bevacizumab within the first trimester when placental growth and fetal organogenesis take place and patient suffered *pregnancy* loss. There is insufficient information to suggest that such use is safe, nor is there definitive evidence to suggest that it causes harm. We advise that ophthalmologists discuss pregnancy with women of childbearing age undergoing intraocular anti-VEGF injections and in pregnant woman counselling is needed to explain the potential risks and benefits.

Keywords Intravitreal vascular endothelial growth factor · Pregnancy · Complication

Introduction

Intravitreal antivascular endothelial growth factor injection is a beneficial treatment for choroidal neovascularization, retinal vascular disorders, diabetic retinopathy (PDR), retinopathy of prematurity and other retinal pathologies [1].

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Recent studies have found that after intravitreal injection of anti-angiogenic agents, these substances *can* enter the *systemic circulation* [2, 3]. In a study conducted on newborn infants, bevacizumab concentration in the serum increased with time after injection into the vitreous cavity [3, 4].

Some female patients are affected by CNV during the child-bearing age and the safety aspects concerning risks for the embryonic and fetal development using anti-VEGF agents such as bevacizumab are of great clinical importance.

Here we describe our experience following intravitreal injection of bevacizumab for the treatment of diabetic retinopathy in a patient during the early unrecognised pregnancy and we provide the first detailed literature review on bevacizumab use during pregnancy.

Case report

A 29-year-old Iranian woman presented with a deterioration of vision in the left eye (LE). *She has* a 10 year *history of* type 1 diabetes mellitus but she has no history of hypertension or dyslipidemia. She is well controlled (diabetes (glycosylated haemoglobin [HbA1c] = 6 %) on regular insulin 15 U three times daily and NPH insulin 20 U/day. She has no diabetes-related complications.

previous gynecologic and medical *history was otherwise unremarkable*.

The both eyes of patient was treated 2 years ago with focal *photocoagulation* for bilateral *macular* edema *and pan-retinal photocoagulation* for bilateral proliferative diabetic retinopathy.

The best corrected visual acuity of the patient's right eye was 6/10 and the left eye was 1/10.

Table 1 Summary of published case reports and registry data on bevacizumab use during pregnancy

Study	Age (years)	Number of Pregnancies Reported	Disease	Time Period of Exposure	Dose/Treatment Regimen	Outcome
Tarantola RM et al. [6]	31-year-old woman	Four cases	subfoveal CNV sarcoid uveitis	Gestational Weeks 17, 21, 26, and 31	2,3	No adverse events
	36-year-old woman		ocular histoplasmosis syndrome	Gestational Weeks 1, 9, 14, 20, 26, and 32.	1,2,3	No adverse events
	33-year-old woman		punctate inner choroidopathy	3 weeks of gestation	1	No adverse events
	27-year-old woman		ocular histoplasmosis syndrome	23 weeks pregnant	2	No adverse events
Sullivan L et al. [11]	20-year-old woman	three cases	CNV associated with punctate inner choroidopathy	at day 19 of gestation	1	No adverse effect
	27-year-old myopic female		CNV associated with punctate inner Choroidopathy	21 days	1	No complication
	A 20-year-old woman		severe proliferative diabetic retinopathy (PDR).	at day 24 of gestation	1	No adverse effect
	25-year-old woman		bilateral PDR and neovascular glaucoma	gestation of 20 days	1	complicated pregnancy in which there was a significant past obstetric history
Introini U et al. [8]	35-year-old woman		subfoveal myopic choroidal neovascularization (CNV)	Week 4	1	No complication
Wu Z et al. [7]	25-year-old woman		myopic choroidal neovascularisation	Weeks 5? Trimester 1	Both eyes were treated with a total of 3 intravitreal injections of bevacizumab	There were no evident pregnancy-related complications at 1 year postpartum.
E Rosen et al. [5]	A 24-year-old myopic woman		CNV and multiple punctate peripapillary and midperipheral hyperfluorescences.	3-month postconception. Trimester 2	1.25 mg bevacizumab	No adverse effect
Petrou P et al. [10]	29-year-old woman	Two cases	bilateral proliferative diabetic retinopathy.	5-week pregnancy	Bevacizumab 1.25 mg)	she suffered an early loss of pregnancy.
	25-year-old woman		choroidal neovascularization in the myopic eye	4-week pregnancy	Bevacizumab 1.25 mg)	she suffered a miscarriage
Sarhianaki A et al. [9]	29-year-old woman		ICNVB	Trimestr 3		No complication

The *anterior segment examination* and intraocular pressure of each eye were within normal limits. *Fundoscopy revealed* the presence of cystoid macular edema in the left eye.

The patient's left eye was then treated with a 1.25 *mg*/0.05 mL intravitreal bevacizumab injection. 18 h after the bevacizumab injection, she reported the vaginal bleeding and ultrasound confirmed a 10-week pregnancy of which the patient was unaware. Patient suffered *pregnancy* loss.

Discussion

Safety data on the use of anti-VEGF agents in pregnant patients are still limited and discussed controversially. Several studies have reported using of intravitreal bevacizumab during pregnancy without complication [5–9]. In contrast,There are several reports of loss of pregnancy after intravitreal injection of bevacizumab [10, 11].

Of these mothers, 9 were treated in trimester 1 and 2 in trimester 2 and one in trimester 3. 2 of the pregnant patients took multiple intravitreal bevacizumab during pregnancy.

3 patients of 14 reported patients had complicated pregnancy following intravitreal bevacizumab including early loss of pregnancy [10, 11].

Currently, there are no reports of fetal abnormalities in pregnant women taking intravitreal bevacizumab. Analyzing the specific risk of intravitreal bevacizumab therapy, overall 15 pregnancies have been reported so far and are summarized in Table 1.

After intravitreal using of all of anti-VEGF agents, drug concentrations were detected measurable in the systemic circulation and Serum VEGF levels were suppressed significantly [12].

Bakri et al. [3] reported after injection of bevacizumab into the vitreous cavity of rabbit eye, the drug can pass through the eye into systemic circulation and suggested that intravitreal injection of bevacizumab could potentially have a systemic effect.

Systemic adverse events included elevated blood pressure, cerebrovascular accidents and death [13, 14].

Although Maternal IgG antibodies are known to cross the placenta, it is not known if bevacizumab crosses the human placenta because adequate or well-controlled studies of pregnant women have not been conducted.

As early as 24-h post intravenous injection of bevacizumab drug was taken up by the fetus in a dose-dependent manner and in early gestation (day 13) bevacizumab was detectable in the developing embryo and transferring continued until the end of pregnancy [15].

In pregnant rabbits, a dose approximately 1 to 12 times the recommended human dose of bevacizumab confirmed teratogenic effect which include an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other adverse effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions [16].

Recent studies suggested that even small amounts of bevacizumab could migrate into the blood circulation and intravitreal injection of bevacizumab may be associated with systemic and ocular side effects.

In conclusion, the current data of registries and case reports do not support an increased risk or safety for intravitreal bevacizumab use during pregnancy or conception. Caution should be taken when anti-VEGF agents are used during pregnancy, and the possibility of ocular side-effects and systemic side-effects should be explained carefully to patients. Experience on large cohorts is still extremely limited and is still awaiting further investigation. Injection of bevacizumab in young women should be performed after determining that the patient is not pregnant; patients should be advised to use birth control after the intravitreal injections. In pregnant patients, the potential risk of anti-VEGF agents should be balanced against the known risks associated with other medical treatment alternatives and the risk of active disease and complications.

Compliance with ethical standards

Conflict of interest Authors do not have any financial interest in the subject matter of this article.

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