Intravitreal Anti-VEGF Injections in Pregnancy: Case Series and Review of Literature

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Abstract

The use of intravitreal antivascular endothelial growth factor (anti-VEGF) injection is gaining wide acceptance as an off-label therapy for diseases that may affect pregnant women. However, these drugs may cause systemic side effects in the mother and fetal harm. This could lead specialists to not administer the drug or women to abort the fetus or to refuse treatment during pregnancy. We report the course of pregnancy in 3 women treated with intravitreal bevacizumab and provide a review of the literature on the use of intravitreal anti-VEGF in pregnancy. Our patients did not have any drug-related adverse event and delivered healthy full-term infants, although one of the women had risk factors for miscarriage. Infants reached all developmental milestones appropriately during infancy. A literature search on the use of intravitreal anti-VEGF injection in pregnancy was undertaken. Data for this review were identified by searches of PubMed and references from relevant articles using the search terms “pegaptanib,” “bevacizumab,” “ranibizumab,” “aflibercept,” “anti-VEGF,” “intravitreal injection,” “pregnant,” “pregnancy,” “abortion,” “miscarriage,” “preeclampsia,” “embryo–fetal toxicity,” “fetal malformations,” “teratogenesis,” “adverse events,” and “maternofetal complications” in multiple combinations. We believe that intravitreal anti-VEGF can be given during pregnancy only when potential benefit to the woman justifies the potential risks to the fetus. When making a decision about whether to give drugs during pregnancy, it is important to consider the timing of exposure and its relationship to windows of developmental sensitivity. We believe that this review will be useful to specialists to inform and possibly treat their pregnant patients.

INTRAVITREAL INJECTIONS of antivascular endothelial growth factor (anti-VEGF) agents have shown excellent results in the treatment of diseases that do not infrequently affect young patients, as choroidal neovascularization (CNV) from etiologies other than age-related macular degeneration,^{1–13} cystoid macular edema associated with uveitis,^{14–16} neovascular glaucoma,¹⁷ and diabetic retinopathy.^{18–21} Therefore, more frequently, specialists have to deal with pregnant women eligible for intravitreal treatment.

VEGF exerts multiple functions, including vasculogenesis and neoangiogenesis^{22,23} and vascular permeability.²³ Animal and human studies have demonstrated a central role of VEGF in the maintenance of fetal and placental vasculature,²² and a reduced VEGF expression was linked with defective embryogenesis and fetal loss in humans.²⁴ Therefore, the use of anti-VEGF potentially may cause spontaneous miscarriage when administered to pregnant women.

VEGF may also have an important effect on blood pressure regulation.²⁵ Two clinical models have demonstrated a link between inhibition of angiogenic growth factor activity

and hypertension.²⁶ Moreover, 2 common side effects of bevacizumab are hypertension^{25–28} and proteinuria.^{25–27} The relationship between VEGF, hypertension, and maternal preeclampsia is poorly understood. Two cases of bevacizumab toxicity that mimic preeclampsia in nonpregnant women have been reported.²⁷

At present, anti-VEGF drugs used in the field of ophthalmology are pegaptanib, ranibizumab, bevacizumab, and recently aflibercept. Pegaptanib (Macugen; Pfizer) is a 28-base ribonucleic acid aptamer, covalently linked to 2 branched 20-kD polyethylene glycol moieties, that was developed to bind and block the activity of extracellular VEGF, specifically the 165-aminoacid isoform (VEGF165).²⁹ Ranibizumab (Lucentis; Genentech) is a fragment of a humanized monoclonal antibody against all VEGF isoforms.²⁹ Bevacizumab (Avastin; Genentech), a humanized, recombinant monoclonal IgG antibody that binds and inhibits all VEGF isoforms, was approved as an adjuvant agent for the treatment of colorectal carcinoma and is also increasingly used as an off-label therapy in the field of ophthalmology.²⁹

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Aflibercept (VEGF Trap-Eye; Regeneron, Bayer) is a 115-kDa recombinant fusion protein consisting of the VEGF-binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1.²⁹

Pegaptanib is designated Pregnancy Category B (no teratogenicity in mice, but human studies are not yet available), while ranibizumab, bevacizumab, and aflibercept have been assigned to Pregnancy Category C by the FDA (animal studies have revealed evidence of embryo–fetal toxicity, but there are no controlled data in human pregnancy).

There is evidence that following intravitreal anti-VEGF administration in humans, the molecules reach the systemic circulation.³⁰ Pegaptanib, ranibizumab, bevacizumab, and aflibercept differ in their molecular weight, structure, and pharmacokinetics.

Avery et al. demonstrated that ranibizumab, bevacizumab, and aflibercept moved rapidly into the bloodstream, but ranibizumab cleared very quickly, whereas bevacizumab and aflibercept demonstrated greater systemic exposure. In addition, ranibizumab had little effect on plasma VEGF concentrations, whereas bevacizumab significantly reduced VEGF in plasma. Despite its serum concentrations being intermediate between ranibizumab and bevacizumab, aflibercept showed the greatest reduction in plasma VEGF, most likely because of the higher affinity of aflibercept for VEGF compared with bevacizumab.

These findings are consistent with those reported by others,³¹ in which a single intravitreal ranibizumab injection was associated with a significant decrease of plasma VEGF levels only after 1 day. No significant changes in serum levels of VEGF were found from 3 to 30 days following intravitreal ranibizumab. Other authors described that a single intravitreal injection of bevacizumab significantly reduced VEGF blood levels for at least 1 month.^{32,33} Zehetner et al. also showed that intravitreal pegaptanib was not associated with a significant decrease of plasma VEGF levels after 7 days and 1 month following injection. These data suggested that fewer systemic effects could be observed following intravitreal pegaptanib or ranibizumab injection. It is not known whether pegaptanib, ranibizumab, bevacizumab, or aflibercept crosses the placenta in pregnant women.

We report the course of pregnancy in 3 women treated with intravitreal bevacizumab (IVB) injection and provide a review of the literature on the use of intravitreal anti-VEGF injection in pregnancy. The main purpose of the study is to provide useful information to specialists to inform and treat their pregnant patients.

Methods

Records of pregnant women treated with intravitreal anti-VEGF seen by the authors were reviewed. To provide a review of the literature on use of intravitreal anti-VEGF injection in pregnant women, we performed a search of all published papers using the PubMed search engine. The key terms that were used were “pegaptanib,” “bevacizumab,” “ranibizumab,” “aflibercept,” “anti-VEGF,” “intravitreal injection,” “pregnant,” “pregnancy,” “abortion,” “miscarriage,” “preeclampsia,” “embryo–fetal toxicity,” “fetal malformations,” “teratogenesis,” “adverse events,” and “maternofetal complications” in multiple combinations. Reference lists were also examined for any additional relevant studies not identified through the search. We limited the search to studies performed on human population.

Results

Three pregnant women were treated with IVB for CNV because of myopic or presumed ocular histoplasmosis syndrome (clinical characteristics of patients are summarized in Table 1). Our patients did not have any drug-related adverse event and delivered healthy full-term infants, although one of the women had risk factors for a miscarriage (age >35 years, previous miscarriage). Infants reached all developmental milestones appropriately during infancy.

To our knowledge, before our review, only 10 papers^{34–43} comprising a total of 18 pregnancies (in 17 women) were published since 2009: bevacizumab was reported in 16 pregnancies (in 15 women) and ranibizumab in 2 pregnancies. Pegaptanib and aflibercept had no reports of being administered in pregnant women.

Altogether, there were 3 reported cases of abortion after use of IVB.^{36,40} Petrou et al. described 2 women who received IVB at about 4 and 3 weeks of gestation, respectively. They had spontaneous miscarriage 7 and 10 days after administration of drug.

Gómez Ledesma et al. also reported a case of spontaneous abortion after a single IVB in a 41-year-old woman. The miscarriage occurred about 7 weeks after the injection.

Sullivan et al. instead reported a case of preeclampsia after use of IVB. IVB was administered at gestation of 20 days and the other 2 IVB were given before conception. An urgent caesarean section at 29 weeks was required for preeclampsia. The infant required intubation for initial bradycardia and respiratory failure. A period of ventilation and supplemental oxygen was required for respiratory distress syndrome and pulmonary hemorrhage. Mild pulmonary stenosis and intraventricular cerebral hemorrhage were observed.

The use of intravitreal ranibizumab during the third trimester has also been reported in 2 pregnancies without complication.^{38,43}

Discussion

The use of anti-VEGF drugs during pregnancy is controversial because they may potentially cause systemic side effects in the mother and fetal harm, as spontaneous miscarriage and preeclampsia.

It is important to emphasize that spontaneous pregnancy loss is a surprisingly common occurrence.⁴⁴ The miscarriage rate in clinically recognized pregnancies is estimated to range from 11% to 16%.^{45–52} These figures do not include reports on unsuspected early pregnancy loss, which varies from 8% to 22%,^{53,54} or the estimated 10% of women who do not contact any health professional after a miscarriage.⁵⁵ In Wilcox's study the total rate of pregnancy loss after implantation, including clinically recognized spontaneous abortions, was 31%.

Given the high baseline rate of miscarriage, it is unclear if the 2 events reported by Petrou et al. were directly related to IVB. However, the short period between the intravitreal injection and spontaneous abortions, as well as the lack of risk factors for miscarriage in both patients, suggest a possible correlation between bevacizumab injection and early loss of pregnancy. In the event reported by Gómez Ledesma et al., it was not possible to determine whether IVB was given a few days before or after the beginning of pregnancy. However, as previously mentioned, an IVB injection was

TABLE 1. CLINICAL SUMMARY

Case	Diagnosis	Anti-VEGF used	Number of injections while pregnant	Gestation period at time of injection	Risk factors for miscarriage	Risk factors for preeclampsia	Pregnancy complications
1	PIC	Bevacizumab	1	3-month postconception	None	None	None
2	Myopic CNV	Bevacizumab	1	2 weeks after last menstrual period	None	None	None
3 ^a	PDR	Bevacizumab	1	4–5 weeks of gestation	None	DM	Miscarriage
4	Myopic CNV	Bevacizumab	1	3 weeks of gestation	None	None	Miscarriage
5	Sarcoid uveitis	Bevacizumab	4	17, 21, 26, 31 weeks of gestation	None	None	None
6	POHS	Bevacizumab	6	1, 9, 14, 20, 26, 32 weeks of gestation	Maternal age >35 years	Maternal age >35 years	None
7	PIC	Bevacizumab	1	3 weeks of gestation	None	None	None
8 ^b	POHS	Bevacizumab	1	23 weeks of gestation	None	None	None
		Bevacizumab	1	36 weeks of gestation			
9	Myopic CNV	Bevacizumab	1	6 weeks of gestation	None	None	None
10 ^a	POHS	Bevacizumab	1	A few days before or after last menstrual period	Maternal age >35 years	Maternal age >35 years	Miscarriage
11	ICNV	Bevacizumab	1	19 days of gestation	None	None	None
12	PIC	Bevacizumab	1	21 days of gestation	None	None	None
13	PDR	Bevacizumab	1	24 days of gestation	None	DM	None
14	PDR	Bevacizumab	1	20 days of gestation	None	DM, HTN	PE
15	DME	Bevacizumab	1	4 weeks + 2 days of gestation	Maternal age >35 years, previous miscarriage	Maternal age >35 years, previous PE, DM, HTN	None
16 ^c	Myopic CNV	Bevacizumab	1	13 weeks + 6 days of pregnancy	Maternal age >35 years, previous miscarriage	Maternal age >35 years	None
17 ^{a,c}	POHS	Bevacizumab	2	During the second and third trimester	None	None	None
18 ^{a,c}	POHS	Bevacizumab	2	During the third trimester	None	None	None
19 ^a	ICNV	Ranibizumab	2	During the third trimester	None	None	None
20 ^a	ICNV	Ranibizumab	1	Eighth month of pregnancy	None	None	None

^aIt is not possible to date back to the proper week in which the drug has been given to the patient.

^bPatient was treated during 2 separate pregnancies for a new onset CNV during the first pregnancy and a recurrence during the second pregnancy.

^cOur patients.

PIC, punctate inner choroidopathy; CNV, choroidal neovascularization; PDR, proliferative diabetic retinopathy; POHS, presumed ocular histoplasmosis syndrome; ICNV, idiopathic choroidal neovascularization; DME, diabetic macular edema; DM, diabetes mellitus; HTN, hypertension; PE, preeclampsia; anti-VEGF, antivascular endothelial growth factor.

associated with a significant decrease of plasma VEGF levels for at least 1 month. In this report, it is even more difficult to establish a correlation between miscarriage and anti-VEGF, because spontaneous abortion rate increases remarkably after 40 years, reaching 41%.⁴⁷ Also in the case of preeclampsia reported by Sullivan et al., it is not clear whether IVB administration during this patient's pregnancy was contributory. The woman had risk factors for preeclampsia (diabetes, hypertension), and preeclampsia affects about 5%–8% of all pregnant women.^{27,56–60} Infant bradycardia, respiratory distress syndrome, and pulmonary and cerebral hemorrhages could be explained with prematurity.

Both spontaneous miscarriages and preeclampsia reported, occurred when IVB had been given within 5 weeks of gestation. However, in other cases when bevacizumab was given within this time frame, no adverse events occurred,^{35,37,41,42} although in 1 case, the woman had risk factors for miscarriage (age >35

years, previous miscarriage) and preeclampsia (age >35 years, previous PE, hypertension, diabetes).⁴² This woman also had received bevacizumab injections a few days before ovulation besides that at 4 weeks + 2 days of gestation. Consequently, patient and fetus were inadvertently exposed to direct or indirect action of the drug for at least the first 2 months of pregnancy.

While IVB was administered after 5 gestational weeks, there were no maternofetal complications.^{34,37,39} Also of note, 2 women were treated with a total of 4 and 6 IVB injections during pregnancy, at 17, 21, 26, and 31 and 1, 9, 14, 20, 26, and 32 weeks of gestation, respectively.³⁷ Neither patient had adverse events related to treatment, and both delivered healthy full-term infants. In the second case, the fetus was large for gestational age and the woman delivered the infant by scheduled cesarean delivery. Given the importance of VEGF for vascular permeability, it might have been expected to have an

intrauterine growth restriction (IUGR) rather than an accelerated fetal growth. Indeed, IUGR occurs when gas exchange and nutrient delivery to the fetus are not sufficient to allow it to thrive in the uterus. Pediatric medical histories showed that the children had mild eczema in the first case and a mild upper respiratory illness in the second case. These disorders are common in infants, so they are not likely related to the use of IVB.

In conclusion, anti-VEGF drugs may potentially cause systemic side effects in the mother and fetal harm. This could lead specialists to not administer the drug or women to abort the fetus or to refuse treatment during pregnancy. There are anecdotal reports of elective abortions to avoid blindness in monocular women (personal communication). No therapy could lead to irreversible visual impairment and a subsequent reduced quality of life of the young woman. Loss of vision in 1 or both eyes is so significant that it has been classified as a 24% or 85% whole person impairment, or disability, respectively.⁶¹

At present, anti-VEGFs have been used only in case report 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 exposures will not be derived from controlled clinical trials, but from observational studies. Therefore, it is important to consider information from all available postmarketing surveillance sources to optimize detection and characterization of the reproductive effects of prenatal drug exposure. Case reports are the most common source of reported congenital anomalies, but can also be the most difficult to interpret. It is critical to be cautious and objective when evaluating isolated case reports, because adverse outcomes tend to be disproportionately reported. Signals based on case reports will need to be further investigated using other pharmacoepidemiologic studies.

The limited clinical experience reported in the literature does not allow us to establish a definite correlation between use of anti-VEGF and maternofetal complications. This lack of information on the safety of drugs used during pregnancy is an issue relevant to both physicians and patients. Until more data in humans is available, it seems reasonable to be cautious when using these drugs during pregnancy, particularly in the first trimester.

It is known that this time is crucial for the fetal development. In humans, susceptibility to teratogens is maximal during organogenesis (3–8 weeks postconception), when the tissue and organs are forming. Although the function and maturation of these organs may be affected at later stages, structural defects usually occur during these early phases of development.⁶² Each tissue and organ of an embryo has a critical period, during which its development may be disrupted. Therefore, potential adverse events in the embryo or fetus may vary in relation to the time at which drugs are administered.

For all these reasons, we believe that intravitreal anti-VEGF can be given during pregnancy only when potential benefit to the woman justifies the potential risks to the fetus. Counseling is needed to disclose the off-label nature of treatment and to explain the potential risks and benefits. When making a decision about whether to give drugs during pregnancy, it is important to consider the timing of exposure and its relationship to windows of developmental sensitivity. It is essential to give attention to calculate the week post-conception, because determining the gestational week of

exposure based on the date of last menstrual period versus the date of conception can produce a 2-week time difference. If the patient is going to proceed with the treatment, we suggest a multidisciplinary approach before and during pregnancy to allow close observation for any potential adverse maternal and fetal events.

A review of published cases showed that more than 50% of women were discovered to be pregnant only after receiving intravitreal anti-VEGF injection. Therefore, pregnancy tests should be ordered routinely before injection.

To our knowledge, this is the first review reporting all articles published about use of intravitreal anti-VEGF in pregnancy. Particular attention was given to any side effect potentially related to anti-VEGF and to the risk factors for maternofetal complications. We sincerely hope that this review may provide useful information to specialists to inform and treat their pregnant patients.

Acknowledgment

V.B.M. is supported by the National Institute of Health [K08EY020530] and Research Preventing Blindness (RPB).

Author Disclosure Statement

No competing financial interests exist.

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Received: May 3, 2015

Accepted: July 30, 2015

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