The use of anti-VEGF agents in pregnancy – which agent should we use?

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Introduction

- VEGF plays an important role in embryogenesis, implantation and placentation
- Disruption to VEGF pathways has been implicated in obstetric complications including pre-eclampsia and miscarriage
- Drug manufacturers and regulators advise to avoid anti-VEGF use in pregnancy unless the benefits outweigh the risks
- There is limited human safety data for anti-VEGF agents in pregnancy

Aim

Apply pharmacokinetic and animal safety data to further understand the risk-benefit analysis of anti-VEGF in pregnancy and to inform agent selection.

Methods

PubMed literature search

FULL TEXT

Results

The transfer of antibodies from the mother to foetus is an active process mediated by the neonatal Fc receptor (FcRN). FcRN is present at very low levels in the first trimester, when risk of major foetal malformations is highest, meaning antibody transfer is very low until the second trimester (Table 1).[1] Agents with an absent or modified Fc fragment have a theoretical reduced placental transfer (Table 2).

Table 1.

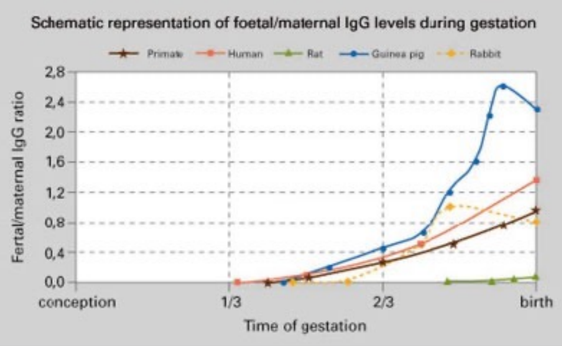
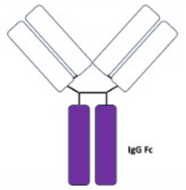
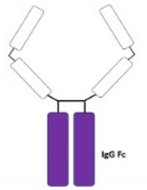
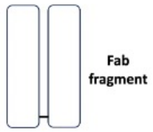
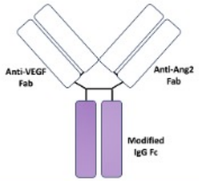


Table 2.

	Anti-VEGF			
	Bevacizumab	Aflibercept	Ranibizumab	Faricimab
Structure			 Fab fragment	
Placental transfer	Crosses placenta		Absent or reduced placental transfer	
Systemic half-life	19 days	11 days	7-9 days	7 days
Systemic VEGF	Reduces systemic VEGF (40-75%)		No significant reduction in systemic VEGF	
Animal safety studies	Rabbits: Teratogenic at all doses		Monkeys: No teratogenic effect	Monkeys: No adverse foetal effects but higher miscarriage rates

Furthermore, FcRN binding protects IgG from degradation, thus prolonging systemic half-life in circulation.[2] Pharmacokinetic studies have demonstrated the effect of intravitreal anti-VEGF on systemic VEGF levels, which is important as suppression of maternal VEGF levels may adversely affect pregnancy.[3]

Animal safety data from rabbits and cynomolgus monkeys is relevant to humans due to their similar placental structure and antibody transfer profiles.[1]

Conclusion

In pregnancy, **Ranibizumab** and **Faricimab** may be preferable due to:

- Reduced potential for placental transfer
- Minimal effects on systemic VEGF
- Shorter half-lives
- Better animal safety study outcomes

References

[1] Pentšuk N, van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal anti-bodies. Birth Defects Res Part B Dev Reprod Toxicol. 2009;86:328–44.
[2] Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007;7:715–25.
[3] Andraweera PH, Dekker GA, Roberts CT. The vascular endothelial growth factor family in adverse pregnancy outcomes. Hum Reprod Update. 2012;18:436–57.