Unconventional treatment of uterine arteriovenous malformation: the challenge of generating evidence for a rare condition

Uterine arteriovenous malformation (AVM) is a rare but serious condition without a universally accepted definition and has a reported incidence of 0.63% after a delivery or abortion. It can lead to heavy uterine bleeding, with significant morbidity. Arteriovenous malformation results from abnormal connections between the uterine arterial and venous systems. Classic treatment options, such as uterine artery embolization and hysterectomy, have serious reproductive implications. Consequently, successful medical treatment options represent a fertility preservation opportunity.

This systematic review sought to quantify and compare the efficacy of medical management options for AVM (1). The investigators also evaluated the factors associated with treatment success and pregnancy outcomes following medical management. They reported a success rate of medical management of as high as 88%. After adjusting for clustering effects, they reported 50% success rates for progestin, gonadotropin-releasing hormone A, and methotrexate. They also reported the lowest adjusted proportion of complications with progestins and gonadotropin-releasing hormone A. Moreover, in 26 subsequent pregnancies, no recurrences of AVM were reported. The key message of this review is to encourage noninvasive, accessible, and cost-effective medical treatment as a first-line option, particularly in stable patients, before considering procedural options (1).

This review is limited by the nature of the studies included in the analysis. This analysis only included 1 prospective, 1 retrospective, and many case reports and case series. Neither randomized controlled trials (RCTs) nor control groups were included. Consequently, the results of this analysis should be interpreted in the context of heterogeneity and a significant publication bias.

Given the lack of RCTs and control groups, with unknown standard success and natural resolution rates, the calculated success rates were based on a comparison with a null hypothesis (50% success rate). This translates to medical management being neither better nor worse than chance alone.

One key takeaway of this review is the unique statistical methodology of this analysis. The investigators used logistic regression within the generalized linear mixed effect regression (GLMR) framework, wherein treatment was included as a fixed effect and a random intercept was included for each investigator to account for clustered responses. Generalized linear mixed effect regression is rarely used in reproductive medicine research despite the fact that it is a part of the standard meta-analysis tool kit. In fact, GLMR has been described as 1 of the 7 models for random effect meta-analyses. In addition, GLMR can result in better statistical inference than the conventional 2-stage approach (2). Using this tool, the investigators strongly believed that the data analysis performed and the statistical tools used warrant classification as a meta-analysis.

This brings to light the challenge of generating evidence for rare conditions. Approximately 8,000 rare conditions have been identified in the European Union and the United States. Many of those are reproductive conditions. In Europe, a condition is defined as rare if the incidence is ≤ 5 per 10,000 people (3). Rare conditions are often heterogeneous in their progression and response to treatment, with only a small population eligible to be included in a study; therefore, novel research methods are required.

Several research methods have been proposed to demonstrate the clinical efficacy of an intervention for a rare disease. Facey et al. (4) recently proposed policies for developing clinical research for rare diseases. The first would be double-blind RCTs, which are considered the gold standard to answer clinical questions. However, for rare diseases, there may be an insufficient patient population to provide the power required to make an RCT feasible, even with multicenter recruitment. Consequently, RCTs can be modified using sequential, 3-stage, or adaptive designs to gain more power from a small patient population while maintaining important design criteria as randomization and blinding and can be analyzed to take into account the multiple analyses performed.

Second, N-of-1 trials use within-patient randomization to test the repeat periods of treatment and control until a response is clear. This approach simply involves double-blind crossover trials in individual patients, with as many crossovers as required until efficacy is established or disproved in the patient. When prospectively planned across several patients and analyzed using Bayesian techniques, a population effect that might be of value can be estimated.

Third, registries with standardized database infrastructure can be an effective tool for the generation of long-term data for a rare condition. They provide insights into the natural history and longer-term outcomes of the condition, such as in a real-world setting. The main challenge of a disease registry is the lack of appropriate controls.

Lastly, patient-reported outcomes can be employed to study rare conditions. Disease-specific measures of functioning and well-being by means of the quality of life are necessary to be designed and validated before their implementation. Similarly, qualitative research can be used to elicit patients' perspectives, with just a small number of patients (4).

In conclusion, this systematic review not only highlights the possibility of employing medical treatment as a treatment option for AVM but also suggests a feasible statistical approach to study such a rare condition. Guidelines on ways to improve evidence for the assessment of

treatment options for rare diseases are necessary. Novel study designs and analyses need standardization and international agreement.

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