A SYSTEMATIC REVIEW OF THE GENETIC LANDSCAPE IN EMPTY FOLLICLE SYNDROME 2018-2023

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Background: Empty Follicle Syndrome (EFS) is characterized by the failure to retrieve oocytes despite apparent normal ovarian stimulation, proper trigger shot injection, and meticulous aspiration of follicular fluid. Cases of EFS have also been described with few markedly abnormal or immature oocytes retrieved.

Objective: Determining the scope of genetic variants found in those diagnosed with EFS may help understand the etiology and help guide future management.

Materials and Methods: Terms “empty follicle syndrome,” “genetics” and “empty follicle syndrome,” “gene” and “empty follicle syndrome,” “variant” and “empty follicle syndrome,” “mutation” and “empty follicle syndrome” were searched in PubMed with a filter set to include articles from 2018 through 2023. 150 articles resulted. Articles that were duplicates, unrelated to EFS, did not include genetic variants, or did not contain a case report were excluded. 29 articles remained describing 91 unique individuals. Gene variants in the articles were confirmed with whole exome sequencing and/or sanger sequencing.

Results: In the 29 reports, 7 genes with 81 gene variants were found to be associated with EFS. Of the 91 patients reported, only 6 pregnancies were achieved with 7 live births (one set of twins). These include 2 of 9 individuals with a variant in the *LHCGR* gene. Conversely, those with variants in the *ZP4* gene (n=1), *TUBB8* gene (n=8), or *PATL2* gene (n=1) did not achieve any pregnancy or live birth. Variants in genes related to the formation or function of the zona pellucida often resulted in no oocytes retrieved or fragile oocytes with a thin or absent zona pellucida. Rates of live birth were low in these individuals; 1 out of 47, 2 out of 14, and 1 out of 11, for *ZP1*, *ZP2*, and *ZP3*, respectively. Proportionally, the live birth rate with *LHCGR* gene variant was higher than any other gene noted in the review. Of note, successful oocyte retrieval was possible in these individuals after prolonging time to oocyte retrieval after trigger between 40 and 50 hours.

Conclusions: Understanding the underlying genetics may help with counseling and potential management in individuals with EFS. For example, given the pregnancies occurred after oocytes were retrieved 40-50 hours after the trigger, it may be worth considering prolonging time from trigger to oocyte retrieval in future patients with *LHCGR* gene variants and EFS. Perhaps, even in patients without a known history of EFS, considering a pause in the oocyte recovery process may be entertained when oocytes are not being retrieved by an experienced operator and EFS is suspected. A few follicles may be left and retrieval interval extended with aspiration of remaining follicles at a prolonged time from trigger.

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