In this study, we examined how self-regulated learning (SRL) and gender influence performance in an educational game for 8th-grade students (N = 130). Crystal Island–Outbreak is an immersive, inquiry-based, narrative-centered learning environment featuring a microbiology science mystery aligned with 8th-grade science curriculum. SRL variables predicted successful in-game performance even after accounting for prior knowledge and perceived gaming skill. Content learning gains were found across both genders, and girls performed at similar levels as boys in the game despite incoming disadvantages for perceived skill and prior gaming experience. Boys were more effective than girls in using a cognitive tool that was critical for solving the Crystal Island–Outbreak mystery; however, these differences disappeared when prior gaming experience was taken into account. Overconfidence on monitoring judgments for boys but not girls was predictive of in-game performance. Findings related to motivational variables such as self-efficacy, situational interest, and goal orientation were mixed with regard to their consistency across genders.

**Keywords:** self-regulated learning, gender, game-based learning, meta-cognition, motivation