

Title: Secondary recurrent miscarriage and H-Y immunity

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Abstract:

**Background:** Approximately half recurrent miscarriage (RM) cases remain unexplained after standard investigations. Secondary RM (SRM) is, in contrast to primary RM, preceded by a birth, which increases the transfer of fetal cells into the maternal circulation. Mothers of boys are often immunized against male-specific minor histocompatibility (H-Y) antigens, and H-Y immunity can cause graft-versus-host disease after stem-cell transplantation. We proposed the H-Y hypothesis that aberrant H-Y immunity is a causal factor for SRM.

**Methods:** This is a critical review of the H-Y hypothesis based on own publications and papers identified by systematic PubMed and EMBASE searches.

**Results:** SRM is more common after the birth of a boy and the subsequent live birth rate is reduced for SRM patients with a firstborn boy. The male:female ratio of children born prior and subsequent to SRM is 1.49 and 0.76 respectively. Maternal carriage of HLA-class II alleles presenting H-Y antigens to immune cells is associated with a reduced live birth rate and increased risk of obstetric complications in surviving pregnancies in SRM patients with a firstborn boy. In early pregnancy, both antibodies against HLA and H-Y antigens are increased in SRM patients compared with controls. Presence of these antibodies in early pregnancy is associated with a lower live birth rate and a low male:female ratio in subsequent live births, respectively. Births of boys are also associated with subsequent obstetric complications in the background population.

**Conclusions:** Epidemiological, immunogenetic and immunological studies support the hypothesis that aberrant maternal H-Y immune responses have a pathogenic role in SRM.