Factors Associated With Subchorionic Hematoma Formation in Pregnancies Achieved Via Assisted Reproductive Technologies

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ABSTRACT

Subchorionic hematoma (SCH) has been reported to be more frequent among singleton in vitro fertilization (IVF) pregnancies than singleton non-IVF pregnancies. This increased prevalence may be due to controlled ovarian hyperstimulation (COH) predisposing the endometrial environment to SCH. Although the exact mechanism leading to SCH is unknown, it is theorized that it may be due to partial detachment of the chorionic membrane from the decidual membrane and may be associated with rupture of blood vessels during villous invasion into the endometrium leading to abnormal placentation. In non-IVF pregnancies, adverse events have been reported as related to SCH including pregnancy loss, abruption, preterm premature rupture of membranes, and fetal growth restriction. Recent data have contested whether SCH is associated with pregnancy loss or adverse outcomes in IVF pregnancies.

This retrospective cohort study aimed to assess whether specific clinical or embryological factors are associated with a greater independent risk of SCH among IVF pregnancies and to potentially suggest a different mechanism by which SCH occurs in such pregnancies. Data were obtained from clinical pregnancies resulting from fresh embryo transfer (ET) at a single fertility center between January 2012 and December 2016. Cases were excluded if they included autologous oocyte frozen ET, donor oocyte cycles, donor embryo cycles, or cases involving a gestational carrier. Individualized protocols based on age and AMH levels were used for COH. Supernumerary good quality blastocysts were cryopreserved on day 5 or 6. Bivariate associations of several clinical measures and embryological laboratory variables were analyzed using 2-variable $\chi^2$ tests, independent samples $t$ tests, and multivariable logistics regression models.

Data were included from 210 IVF clinical pregnancies, of which 117 qualified as blastocyst stage ET. A significant bivariate association was found between trophectoderm (TE) grading and SCH, as 41.82% of pregnancies with TE grade B or C having SCH compared with 20.97% of TE grade A [$\chi^2(1) = 5.95, P = 0.015, n = 117$]. There was also evidence of bivariate association between SCH and final p4, defined as peak progesterone level on day of trigger, with the SCH group having a lower final p4 value ($P = 0.043$). Multivariable logistics regression modeling showed that, in cases where TE was performed (n = 113), the TE grade was the only statistically significant predicting factor of SCH and revealed that pregnancies receiving a grade of A had a 75% reduced odds of SCH when adjusting for other factors (adjusted odds ratio, 0.25; 95% confidence interval, 0.09–0.68; $P < 0.01$). No difference was detected in spontaneous miscarriage rate between IVF pregnancies with and without SCH.

The results of this study suggest that a lesser TE grade (B or C) increases the odds of SCH occurring in IVF pregnancies, and this association remained when adjusting for several potential confounding factors. Given the small sample size of 113 pregnancies with a full data set, this finding suggests this is a notable relationship with a large effect size.

EDITORIAL COMMENT

(Subchorionic hematoma is a frequent complication of singleton IVF pregnancies. Prior studies showed that disruption of the endometrium by ovarian hyperstimulation (COH) may promote SCH by facilitating partial detachment of the chorionic from the decidual membrane and rupture of blood vessels during villous invasion into the endometrium. This abnormal placentation also may contribute to other adverse events associated with SCH, including pregnancy loss, abruption, preterm...
premature rupture of membranes, and fetal growth restriction.

This retrospective cohort study looked at whether clinical and embryological also contribute to SCH. Bivariate and multivariate logistic regression methods were used. Bivariate analysis showed that TE grade and peak progesterone level on the day of trigger (with the SCH group having a lower value) were associated with SCH. Multivariable logistic regression modeling showed that, after controlling for other factors, TE grade was the only statistically significant predictor of SCH. Grade of A TE conferred a 75% lower odds ratio for SCH. Thus, suboptimal TE development seems to increase the risk of SCH in IVF pregnancies. This fascinating study will stimulate additional research on the effects of IVF on TE and TE on SCH as well on other pregnancy-related complications after assisted reproduction.—DK)