Göteborg, 2020

Long-term outcome of children born after Assisted Reproductive Technology

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal K2320 C Kylberg, Medicinaregatan 7, den 4 december, klockan 13.00

av Emma Norrman

Fakultetsopponent:
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Avhandlingen baseras på följande delarbeten

I. Norrman E, Petzold M, Bergh C, Wennerholm UB. School performance in singletons born after assisted reproductive technology. *Hum Reprod* 2018;**33**:1948-1959.

II. Norrman E, Petzold M, Bergh C, Wennerholm UB. School performance in children born after ICSI. *Hum Reprod* 2020;**35**:340-354.

III. Norrman E, Petzold M, Clausen TD, Henningsen AK, Opdahl S, Pinborg A, Rosengren A, Bergh C, Wennerholm UB. Type 1 diabetes in children born after assisted reproductive technology: a register based national cohort study. *Hum Reprod* 2020;**35**:221-231.

IV. Norrman E, Petzold M, Gissler M, Spangmose AL, Opdahl S, Pinborg A, Henningsen AK, Tiitinen A, Rosengren A, Romundstad LB, Wennerholm UB Bergh C. Cardiovascular disease, obesity and type 2 diabetes in children born after assisted reproductive technology: a population based cohort study. *In manuscript.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Long-term outcome of children born after Assisted Reproductive Technology

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Abstract
Background: While the short-term outcome after assisted reproductive technology (ART) is broadly examined, studies on the long-term outcome of ART children are limited.
Aim: To examine the long-term outcome in children born after ART and study whether different ART techniques affect the outcome in the children differently.
Material and methods: All papers were national population-based register studies, performed by cross-linking national ART registers with health data registers. *Paper I-III* included all singletons born in Sweden: after ART (n=8 323) and spontaneous conception (SC) (n=1 499 667) between 1985 and 2001 *(Paper I),* after ICSI (n=6 953), IVF (n=11 713) and SC (n=2 022 995) between 1985 and 2006 *(Paper II)* and after ART (n=47 938) and SC (n=3 090 602) between 1985 and 2015 *(Paper III).* In *Paper IV* all singletons born after ART (n=122 429) and SC (n=7 574 685) in Sweden, Norway, Finland and Denmark between 1984 and 2015 were included. The primary outcomes were school performance (*Paper I and II*), type 1 diabetes *(Paper III)*, cardiovascular disease, obesity and type 2 diabetes *(Paper IV).*
Results: *Paper I:* ART children had significantly better school results than SC children in the crude analyses. After adjustment, a small but significant difference was observed in total scores in favour of SC children (adjusted mean difference [percentiles] -0.72; 95% confidence interval -1.31 to -0.12; p=0.018). *Paper II:* ICSI children had similar school performance as IVF and SC children in the ninth grade. In the third grade, ICSI children had lower chance of passing all the subtests in mathematics and Swedish compared to SC children. *Paper III:* ART children had no increased risk of type 1 diabetes after adjustment for important covariates. In a subgroup analysis, children born after frozen embryo transfer had increased risk of type 1 diabetes compared to children born after fresh embryo transfer and SC. *Paper IV:* No increased risk of cardiovascular disease or type 2 diabetes were found among ART children in the adjusted analyses. A small but significantly increased risk of obesity was found.
Conclusion: School performance up to ninth grade is reassuring for ART children. Cardiometabolic outcomes in ART children are also generally reassuring. However, the number of events were limited for several diseases and small negative differences were observed in a few analyses. Previous studies of ART children have repeatedly suggested small differences in cardiometabolic surrogate outcomes, emphasizing a need for further studies.
Keywords: assisted reproductive technology, IVF, children, long-term outcome, school performance, neurodevelopmental, diabetes, cardiovascular disease, obesity

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