**The risk of cerebral palsy in ART children has more than halved over two decades – a Nordic collaborative study on 55,233 liveborn children**
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**Study question:**

Has the risk of cerebral palsy (CP) changed over a 20-year period in children born after assisted reproductive technology (ART)?

**Summary answer:**

Over two decades, the risk of CP in ART-children decreased with more than 50%, mainly due to single embryo transfer resulting in lowering twin rates.

**What is known already:**

During the last two decades we have seen a considerable reduction in twin birth rates after ART treatment in Europe herein the Nordic countries. In the Nordic countries, the twin births rates in ART pregnancies have declined from almost 25% two decades ago to less than 5%, compared with 2–3% in the background population of spontaneously conceived (SC) pregnancies. Concomitantly the preterm birth (PTB) rate has diminished considerably. PTB increases the risk of CP, which is one of the most severe complications in ART-children with long term consequences for the children and their families.

**Study design, size, duration:**

A Nordic registry-based cohort study using data from Denmark (birth years 1994–2010) and Finland (1990–2010) including two cohorts: 55,233 ART-children and 2,327,350 SC-children. Among the ART-children, 37,404 were singletons, 17,057 were twins and 772 were higher order multiples. We investigated the risk of CP in the following time periods: birth year 1990–1994, 1995–1999, 2000–2004 and 2005–2010. Children were followed up until 2014.

**Participants/materials, setting, methods:**

Data originated from the CoNARTaS cohort (Committee of Nordic ART and Safety) containing information from national ART- and patient registries. CP was defined as G80 ICD-10-diagnoses registered in the patient registry before the age of ten. Risk of CP was compared for ART vs. SC children, singletons and twins using logistic regression models. Adjustments were made for maternal age, parity, child’s sex, country and birth year as well as plurality (if applicable).

**Main results and the role of chance:**

Overall, 307 (0.6%) ART- and 5,911 (0.3%) SC-children were diagnosed with CP. During the study period the crude risk of CP in ART-children decreased consistently from 0.9% (1990–1994) to 0.4% (2005–2010), while the risk remained unchanged for SC-children (0.3%). For ART-singletons the risk of CP decreased from 0.7% (1990–1994) to 0.3% (2005–2010), but remained stable for ART-twins (0.7%), SC-singletons (0.2%) and SC-twins (0.8%).
Throughout the study period the adjusted risk of CP was higher for ART- versus SC-children (adjusted odds ratio [aOR] 1.93 [95%CI 1.71;2.17]). The risk remained increased after further adjustment for plurality (aOR 1.18 [95%CI 1.04;1.34]). The risk of CP was higher for ART-singletons (aOR 1.32 [95% CI 1.10;1.57]) but similar for ART-twins compared with their SC counterpart.
Analyses stratified on birth year showed a consistent decrease in risk of CP over time for ART- versus SC-children (1990–1994: aOR 2.88 [95%CI 1.81;4.32]; 2005–2010: aOR 1.34 [95%CI 1.12;1.61]). In 2005–2010 the risk of CP, after further adjustments for plurality, was no longer statistically significant (aOR 0.96 [95%CI 0.79;1.15]). Additionally, the risk of CP decreased substantially over time for ART-singletons compared with SC-singletons (1990–1994: aOR 2.53 [95%CI 1.20;4.63]; 2005–2010: aOR 1.21 [95%CI 0.88;1.62]).

**Limitations, reasons for caution:**

Observational studies may have inadequate adjustment for potential confounding factors. Despite adjustment for some major confounders, residual confounding cannot be excluded.

**Wider implications of the findings:**

Limiting the number of twins born after ART treatment lowers the risk of CP in the ART population. Multiple embryo transfer is still the standard care in many countries. Our findings emphasize that single embryo transfer should be encouraged worldwide.

**Trial registration number:**-
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