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IVF for male infertility linked to increased risk of intellectual disability and autism in children

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In the first study to compare all available IVF treatments and the risk of neurodevelopmental disorders in children, researchers find that IVF treatments for the most severe forms of male infertility are associated with an increased risk of intellectual disability and autism in children.

Autism and intellectual disability remain a rare outcome of IVF, and whilst some of the risk is associated with the risk of multiple births, the study provides important evidence for parents and clinicians on the relative risks of modern IVF treatments.

Published in *JAMA* today, the study is the largest of its kind and was led by researchers at King's College London (UK), Karolinska Institutet (Sweden) and Mount Sinai School of Medicine in New York (USA).

By using anonymous data from the Swedish national registers, researchers analysed more than 2.5 million birth records from 1982 and 2007 and followed-up whether children had a clinical diagnosis of autism or intellectual disability (defined as having an IQ below 70) up until 2009. Of the 2.5m children, 1.2% (30,959) were born following IVF. Of the 6,959 diagnosed with autism, 103 were born after IVF; of the 15,830 with intellectual disability, 180 were born after IVF. Multiple pregnancies are a known risk factor for pre-term birth and some neurodevelopmental disorders, so the researchers also compared single to multiple births.

Sven Sandin, co-author of the study from King's College London's Institute of Psychiatry says: "IVF treatments are vastly different in terms of their complexity. When we looked at IVF treatments combined, we found there was no overall increased risk for autism, but a small increased risk of intellectual disability. When we separated the different IVF treatments, we found that 'traditional' IVF is safe, but that IVF involving ICSI, which is specifically recommended for paternal infertility is associated with an increased risk of both intellectual disability and autism in children."

Compared to spontaneous conception, children born from any IVF treatment were not at an increased risk of autism, but were at a small increased risk of intellectual disability (18% increase – from 39.8 to 46.3 per 100,000 person years). However, the risk increase disappeared when multiple births were taken into account.

Secondly, the researchers compared all 6 different types of IVF procedures available in Sweden – whether fresh or frozen embryos were used; if intracytoplasmic sperm injection (ICSI) was used, and if so, whether sperm was ejaculated or surgically extracted. Developed in 1992, ICSI is recommended for male infertility and is now used in about half of all IVF treatments. The procedure involves injecting a single sperm directly into an egg, rather than fertilization happening in a dish, as in standard IVF.

Children born after IVF treatments with ICSI (with either fresh or frozen embryos) were at an increased risk of intellectual disability (51% increase – 62 to 93 per 100,000). This association was even higher when a preterm birth also occurred (73% increase – 96 to 167 per 100,000). Even when multiple and pre-term births were taken into account, IVF treatment with ICSI and fresh embryos was associated with an increased risk of intellectual disability (66% increase for singleton birth, term birth following ICSI with fresh embryos– 48 to 76 per 100,000).

Children born after IVF with ICSI using surgically extracted sperm and fresh embryos were at an increased risk of autism (360% increase - 29 to 136 per 100,000) but the association disappeared when multiple births were taken into account.

Dr Avi Reichenberg, who led the study from King's College London's Institute of Psychiatry and Mount Sinai School of Medicine, adds: "Our study shows that treatments developed to manage male infertility are associated with an increased risk for developmental disorders in the offspring. The exact mechanism is unclear, but there are a number of risk factors, from selection of IVF procedures, to multiple embryos, and to preterm birth. Whilst intellectual disability or autism remain a rare outcome for IVF, being aware of the increased risk associated with specific types of IVF means offspring at risk can be identified and potentially monitored for developmental disorders, ensuring they receive early detection and appropriate support and care."

Dr Karl-Gösta Nygren, co-author from Karolinska Institutet, says: "It's important to remember that the majority of children are born perfectly healthy following IVF. Our study provides much needed information for parents and clinicians on the relative risks of modern IVF treatments, enabling them to make the most informed choice possible. Our study also provides further evidence for the need to minimize multiple embryo transfer. However, more research is needed to elucidate the reasons behind our findings."

The authors add that within the context of this study, it was not possible to determine the exact mechanism by which IVF treatment following ICSI is associated with an increased risk of intellectual disability. However, the authors did extend their study to consider possible explanations for the increased risk, such as parental age, temporal trend, hormonal treatment or length of infertility problems, but found no further explanations to the results.

The study was conducted in Sweden but the findings are applicable to most countries where IVF and ICSI are used but there may be differences in choice of procedure.

More information: Sandin, S. et al. "Autism and Mental Retardation Among Offspring Born After In Vitro Fertilisation" *JAMA* (2013; 310(1):75-84, 3rd July 2013)

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