ESHRE 2021 Virtual (26 June-1 July 2021)

Questions for the speakers

Session 02: Safety follow-up on ART children; data from infant to young adult

Markers of cardiometabolic health of adolescents conceived through assisted reproductive technologies (ART) appear reassuring - Laura Wijs (Australia)

Q: Do leaner offspring mean that mothers were likely to be of lower BMI than other women of same age in Australia?

A: This could be a possible explanation. Unfortunately, we do not have information on maternal BMI at time of conception and have therefore not been able to take this factor in to account. Parental cardiometabolic health may affect offspring cardiometabolic health, hence it would be useful if future studies could take BMI and other parental health factors in to account.

Q: Do you know if the participants you recruited had differences in embryo culture conditions? (medium/oxygen)

A: We do have information on embryo culture for some of the participants, but not for all. Unfortunately, the numbers are too low to analyze any effect of different culture media used.

Q: Any idea if the presence of PCOS in mothers had any influence?

A: We ran additional analyses to investigate a potential association between parental cause of infertility (among which PCOS) and cardiometabolic outcomes in the offspring, and found no statistical differences. However, numbers would have been too low to detect any differences and therefore we cannot draw any conclusions based on our data. It would be interesting if future studies could investigate this further, as PCOS may affect maternal metabolic health, which may in turn negatively affect the cardiometabolic health of their children.

Q: Why do you think the cause of cardiometabolics and icsi?

A: ICSI in particular has been associated with epigenetic alterations, which may explain an increased risk of an unfavorable cardiometabolic profile in ICSI offspring. We compared ICSI and IVF within our ART cohort, and found no significant difference, however these analyses were lacking statistical power and therefore we cannot draw any conclusions on this question.

Q: BMI is often related to socio economic status; did you take this parameter into account ?
A: Yes, socio-economic status did not differ between the cohorts in our study, therefore we did not adjust for socio-economic status.

The association between high birth weight and long-term outcomes-implications for Assisted Reproductive Technologies: a systematic review and meta-analysis - Åsa Magnusson (Sweden)

Q: Do you think the method of endometrium preparation for FET can influence birthweight and later development?

A: Only a few studies have investigated the association between perinatal outcomes and different endometrial preparation regimens. (Ernström Ginstad et al 2019 found a significant increased risk of macrosomia and post-term pregnancy in programmed cycle compared to stimulated cycle or natural cycle and the same association was found by Asserhøj et al 2021 in programmed cycles compared to natural cycles. On the other hand, Li et al 2021 found a significant risk of LBW in HRT cycles compared to natural cycles. Further studies are needed to investigate if different endometrial preparation regimens have an impact on short term and long-term outcomes perinatal outcomes.

Q: Clearly future analyses need to separate FET babies from non -FET babies. Would you please comment?

A: Yes, I agree. We still don´t know if there is a difference in long term health outcomes as a consequence of high birth weight/LGA when comparing FET cycles to fresh cycles or comparing ART cycles to spontaneous pregnancies

Q: Are the long term health issue related to HBW/LGA in births obtained after ART different form those in births from spontaneous pregnancies ?

A: Since FET is a relatively new technique in ART compared to fresh cycles, there still are no studies investigating long term health outcomes in adults born LGA or with a high birth weight after FET. However, the FET rate is increasing worldwide and it is of great importance to follow up on long term health outcomes after FET and also to study if there is a difference being born LGA or with a high birth weight after FET compared to after spontaneous pregnancy

Q: Is there an association with complications in pregnancy? like pre-eclampsia/hypertension, diabetes etc.

A: In this study we did not investigate obstetric outcomes

Q: Did these studies adjust for parental characteristics and maternal co-morbidities such as gestational diabetes mellitus?

A: Our study was a systematic including of a large number of studies where there was a large heterogenicity in confounders adjusted for. Mother´s co-morbidity was adjusted for in some studies

Q: Are children coming from FET in spontaneous cycles separate from stimulated one?

A: Our study investigates the association between high birth weight and LGA and long-term health outcomes in general. There are still no studies investigating the association between high birth weight/LGA and long-term health outcomes in ART cycles specifically.

Q: Based on your study, do you or would you provide patients this information pre-treatment?

A: Yes, in my opinion we, as clinicians, are obliged to provide our patients with evidence-based information and to consider the aspects of safety and efficacy whenever we suggest and plan a specific treatment

Q: Could the HBR and LFGA and their health problems not be the result of the health of the mothers?

A: Yes. Studies have shown that the incidence of LGA/high birth weight increases over time as a consequence of increasing prevalence of obesity in the population. It is also well known that diabetes and gestational diabetes increase the risk of high birth weight/LGA. Furthermore, offspring of women with PCOS have shown to have an altered cardiometabolic profile (Gunning et al 2020) and various other diseases (Doherty et al 2016). However studies investigating the association between diabetes in mothers and LGA/high birth weight in offspring were excluded in our review.

Neurodevelopmental morbidity in children born after ART: a Nordic register study from the Committee of Nordic ART and Safety (CoNARTaS) group - Kristiina Rönö (Finland)

Q: Several studies suggested a relation between ASD and delivery route (caesarian versus vaginal). Did you take this factor into account?

A: The mode of delivery was not included in the model

Q: Was there a correction for de delivery term for the difference in learning disorders?

A: In the presentation the Model did not include gestational age. It is important to be cautious when adjusting for gestational age, as it can be considered a mediator on the causal pathway of type of ART and neurodevelopmental disorders, causing bias. We have, however, performed the analyses with model that additionally includes gestational age at delivery (continuous) as a confounder, and the results are quite similar.

Q: Was data on duration of progesterone exposure available?

A: The data on details of progesterone use (nor any other medications or hormones used), are not available on the registries

Q: Do you think female BMI could be an important factor to consider?

A: We agree, BMI might be an important factor. Unfortunately, in the registries considerable proportion of the mothers are missing the information, especially concerning the oldest cohorts. Therefore, it is not possible to consider it as a confounder.

Q: With these results, what do you advice in counseling couples starting ART-treatment

A: Our results are reassuring and support prior literature of mostly comparable neurodevelopment between ART and spontaneously conceived children when it comes to singleton pregnancies. When differences are seen (as in Learning and motor functioning disorders; F80-83), in absolute numbers, these risks are not particularly significant either. Most of the studies reporting association with neurodevelopmental disorders, have included considerable proportions of twins or higher order multiples. Pregnancies with multiples are in higher risk for preterm delivery and other pregnancy complications that can mediate the association.

Q: Were the parents checked for neurodevelopmental disorders? ADHD for example was not checked or diagnosed in people above 35years.

A: We are only able to control for parental ever history of any psychiatric morbidity (meaning following diagnostic codes as a group: ICD-8/9: 290–319, ICD-10: F01–99). The neurodevelopmental diagnoses of adults or lack of them, especially during the earliest cohorts (and those of women) of CoNARTaS, cannot be considered reliable due to changes in diagnostic practices.