

Norwegian Institute of Public Health - Centre for Fertility and Health – impact case number 2

Institution: Norwegian Institute of Public Health
Administrative unit: Centre for Fertility and Health
Title of case study: Assisted reproductive technologies and impact on women's and children's health
Period when the underpinning research was undertaken: 2017 - 2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2017 - 2023
Period when the impact occurred: 2018-2023

1. Summary of the impact

Women using Assisted Reproductive Technologies (ART) and children born after ART have been found to have increased risk of some adverse health outcomes. Our studies find that the actual ART procedures may play a role, and that some risks may vary with procedures, while others do not. Our research informs fertility clinicians and couples considering ART about potential risks, and helps clinicians and couples consider the safest ART method for them.

2. Underpinning research

With interdisciplinary teams, international collaborations and data from health registries and the Norwegian Mother, Father, and Child Cohort Study (MoBa), we have shown that (dates of when research was carried out in parentheses):

- 1) Women using ART differ in characteristics from women conceiving naturally (Jan 2019 to Jun 2020)
- 2) The long-term risk of cardiovascular diseases is not increased in women using ART (Jan 2021 to Sept 2023), and there are small cardiovascular differences in children born after ART (Jan 2020 – Jul 2022)
- 3) There is increased risk of preterm delivery and neonatal death after ART (Aug 2018 – Feb 2023)
- 4) ART-conceived children have increased risk of respiratory infections (Aug 2020 to Aug 2022) and are different in growth up to age 7 but not at age 18 (Mar 2020 – Mar 2021). The differences in birth weight were partly mediated through DNA methylation (Jun 2021 – Nov 2022)
- 5) ART-conceived offspring have fewer children as young adults, but not higher risks of pregnancy complications (Aug 2021 – Nov 2022)
- 6) ART conceived children have DNA methylation differences at birth in 176 known genes (Nov 2017 – Jul 2022), including differences in the BRCA promotor gene and in genes on the X chromosome (Jul 2020 – Jul 2022)

We are now following up and exploring if DNA methylation differences persist into childhood, and whether they are associated with RNA expression, sex differences in DNA methylation, and effects on outcomes.

Underpinning projects, funding and OUTPUT

Our work underpinning the impact of our ART research, is based on several research projects and funding:

1. The Norwegian Research Council's Centre of Excellence funding scheme (#262700)
OUTPUT: Researcher time, PhD, Costs for analyses of DNA methylation
2. The European Research Council Starting Grant INFERTILITY (#947684)
OUTPUT: Data collection, researcher time

3. The Norwegian Cancer Society) (#244291-2022)
OUTPUT: Data collection, researcher time, analyses of RNA and DNA methylation
4. Norwegian Institute of Public Health (own funding)
OUTPUT: Data collection, researcher time, infrastructure

NAME OF RESEARCHER	POSITION	DATE JOINING	DATE LEAVING
Siri Eldevik Håberg	Director	Nov 1, 2017	-
Per Magnus	Deputy Director	Nov 1, 2017	-
Øystein Kravdal	Principal Investigator	Nov 1, 2017	-
Liv Bente Romundstad	Researcher	Feb 1, 2018	-
Hans Ivar Hanevik	Researcher	Apr 8, 2019	-
Maria C Magnus	Senior Researcher	Aug 1, 2018	-
Astanand Jugessur	Senior Researcher	Nov 1, 2017	-
Håkon Gjessing	Principal Investigator	Nov 1, 2017	-
Yunsung Lee	Researcher	Nov 1, 2017	-
William Denault	PhD/Postdoc/Researcher	Jan 1, 2018	August 31, 2022
Haakon Nustad	Researcher	Jul 1, 2020	-
Christian Page	Researcher	Nov 1, 2017	-
Kristine Løkås Haftorn	PhD research fellow	Feb 1, 2019	June 30, 2023
Robert Lyle	Researcher	Apr 3, 2020	-
Ellen Øen Carlsen	PhD research fellow/Postdoc	Mar 4, 2019	-
Julia Romanowska	Postdoc/Researcher	Nov 1, 2017	-
Miriam Gjerdevik	PhD/Postdoc/Researcher	Nov 1, 2017	-

More than 10 million children have been born worldwide after ART. The number is rapidly increasing, also in Norway, where more than 50 000 children have been conceived through ART since 1984. Studies have found that these children have lower birthweight, higher risk of neonatal complications and increased risk of certain diseases, such as metabolic and neurodevelopmental disorders as well as some cancers.

It has been difficult to study whether these increased risks are related to the ART procedures or to the underlying conditions causing subfertility. Most studies have had methodological shortcomings, such as limited sample sizes and relatively short follow up time. A challenge in studying potential links between ART and risk of cancer beyond childhood is the relatively young age of the ART-conceived group. Although current evidence suggests a higher risk of some cancers in children born after ART it is emphasized that it is still unknown whether this is due to the ART treatment, to birth outcomes associated with ART, or to other factors associated with the use of ART, including parental subfertility. Our research is aimed at resolving these questions.

3. References to the research

- Goisis A, Håberg SE, Hanevik HI, Magnus MC, Kravdal Ø. (2020). The demographics of assisted reproductive technology births in a Nordic country. *Hum Reprod*, 35(6), 1441-1450. <https://doi.org/10.1093/humrep/deaa055>
- Magnus MC, Fraser A, Håberg SE, Rönö K, Romundstad LB, Bergh C, Spangmose AL, Pinborg A, Gissler M, Wennerholm UB, Åsvold BO, Lawlor DA, Opdahl S. (2023). Maternal Risk of Cardiovascular Disease After Use of Assisted Reproductive Technologies. *JAMA Cardiol*, 8(9), 837-845. <https://doi.org/10.1001/jamacardio.2023.2324>
- Magnus MC, Wilcox AJ, Fadum EA, Gjessing HK, Opdahl S, Juliusson PB, Romundstad LB, Håberg SE. (2021). Growth in children conceived by ART. *Hum Reprod*, 36(4), 1074-1082. <https://doi.org/10.1093/humrep/deab007>

4. **Carlsen EØ, Lee Y, Magnus P, Jugessur A, Page CM, Nustad HE, Håberg SE, Lie RT, Magnus MC.** (2022). An examination of mediation by DNA methylation on birthweight differences induced by assisted reproductive technologies. *Clin Epigenetics*, 14(1), 151. <https://doi.org/10.1186/s13148-022-01381-w>
5. **Carlsen EØ, Wilcox AJ, Magnus MC, Hanevik HI, Håberg SE.** (2023). Reproductive outcomes in women and men conceived by assisted reproductive technologies in Norway: prospective registry based study. *BMJ Med*, 2(1), e000318. <https://doi.org/10.1136/bmjmed-2022-000318>
6. **Håberg SE, Page CM, Lee Y, Nustad HE, Magnus MC, Haftorn KL, Carlsen EØ, Denault WRP, Bohlin J, Jugessur A, Magnus P, Gjessing HK, Lyle R.** (2022). DNA methylation in newborns conceived by assisted reproductive technology. *Nat Commun*, 13(1), 1896. <https://doi.org/10.1038/s41467-022-29540-w>

4. Details of the impact

The nature and extent of the impact

The research increases knowledge about risk factors for cancer and consequences of ART treatments. More information on potential risks will enable couples to make more informed choices about reproduction and use of ART. This is important as use of ART is increasing. Our results identify risks according to different ART methods and in specific subgroups of women. This may guide medical practice and help tailor treatments.

The results increase the understanding of the role of genetics and epigenetics in breast cancer and other *BRCA*-associated cancers. Better knowledge on longer term health risks in persons conceived by ART will provide opportunities for closer follow-up and tailored screening and may inform preventive measures and early detection of cancer. This may improve the prognosis and potentially give rise to personalized treatment.

Researchers at our unit have collaborated with several institutions in the described work. One collaboration was through the CoNARTaS – the Committee of Nordic Assisted Reproductive Technology and Safety. Our collaborative work with ConARTAS has been presented at scientific conferences.

1. Magnus MC *et al.* Maternal risk of cardiovascular disease after use of assisted reproductive technologies: a Nordic registry linkage. *Society of Pediatric and perinatal Epidemiological Research, Chicago, June, 2022. Poster Presentation 0093.*
2. Westvik KJ *et al.* Maternal and treatment contributions to perinatal outcomes after transfer of fresh and cryopreserved embryos in assisted reproduction: A Nordic sibling study. *European Society of Human Reproduction (ESHRE) virtual meeting in 2020. Oral Presentation O-029.*

Our unit's work with epigenetics after ART have been disseminated at several scientific meetings as posters and oral presentations:

1. **Lyle R *et al.*** START: The Study of Assisted Reproductive Technologies. *European Society of Human Genetics (ESHG) Conference (2020)*. Interactive e-poster P01.005.B
2. **Lyle R *et al.*** DNA methylation in newborns conceived by assisted reproductive technology. *European Society of Human Genetics (ESHG) Conference (2022)*. Hybrid Poster P01.024.D.
3. **Lyle R *et al.*** Assisted Reproductive Technology is associated with DNA Methylation in Newborns Conceived by Assisted Reproductive Technology. *Wellcome Genome Campus, UK, November 2021*. Oral Presentation.

4. **Lyle R et al.** DNA methylation in newborns conceived by assisted reproductive technology. *Genetics of Reproduction Meeting. The Royal Society, London (2022). Poster P01.*

Beneficiaries of the impact

Scientific community: Research findings has been communicated to the international scientific community through publications in high impact journals and by presentations at scientific conferences. The findings generate future research questions and collaborations with the obstetric community and perinatal epidemiologists, as well as with researchers in cancer, assisted reproduction, genetics, and epigenetics.

Policy makers: The Norwegian Institute of Public Health (NIPH) is in direct frequent contact with governmental agencies, and we communicate relevant findings to policy makers, such as the Directorate of Health and the Ministry of Health and Care Services. Our research has had an impact through public media. By identifying robust modifiable factors that influence the risk of breast cancer or other cancers after ART, this knowledge can be used to guide interventions and develop screening tools and treatments. The results from this project will help guide future research efforts in this direction.

Clinicians: We collaborate closely with two public and one private fertility clinic in Norway. These collaborators have central roles in the medical field of ART in Norway, and they ensure close contact and communication of results to clinicians and obstetricians. Presentations have been given to clinicians participating in annual meetings of their National Association (NOFAB). We have also presented our work at a network conference to clinicians and researchers within breast cancer research (see dates and meetings below).

The general public: We participate in open popular science meetings to communicate research findings, for example the “Women’s health conference”. Also, we communicated our findings through open popular research websites specifically designed to communicate science to a general audience (project descriptions at www.fhi.no and www.cefh.no).

Subfertile women, women using ART and breast cancer patients: Our clinical collaborators are in close contact with representatives from the Norwegian Association for Fertility and Unwanted Childlessness “Ønskebarn” and will be involved in communicating results to women who struggle to conceive. This will ensure the right communication to those who consider ART or are treated with ART and to those who may face increased risk of adverse effects and adverse health conditions as a consequence of their infertility. Our results have been presented to patients through user participation at Women’s health conference and NOFAB (see dates and meetings below).

5. Sources to corroborate the impact

Public popular science presentations for clinical and general audience:

1. Norwegian Association of Assisted Reproduction (NOFAB). Invited presentation. Annual meeting, Nov 2022. Håberg, SE. DNA methylation in newborns conceived by ART.
2. Norwegian Association of Assisted Reproduction (NOFAB). Invited presentation. Annual meeting, Nov 2019. Håberg, SE. Centre for Fertility and Health, studies on ART.
3. Women’s Health Conference (Kvinnehelsekonferansen), Norwegian Research Council, Research on Women’s Health, Dec 2022. Håberg, SE.

4. National Network Conference on Breast Cancer Research (research groups and breast cancer society), January 14, 2023, Trondheim, Norway. Invited presentation. Håberg SE. Risk of breast cancer in persons born after assisted reproductive technologies.