



Invitation to PhD defence

Ditte Vassard



Assisted reproductive technology treatment and risk of death, ovarian cancer and breast cancer

- Date** Wednesday, February 26, 2020 at 14:30 hrs.
- Venue** Room 1.1.18, Center for Health and Society (CSS), University of Copenhagen, Øster Farimagsgade 5, DK-1353 Copenhagen K
- Reception** A reception will be held after the defence at the Section of Social Medicine, Gothersgade 160, 3rd floor left, DK-1123 Copenhagen K

Academic advisors

- Professor wsr Lone Schmidt, Section of Social Medicine, Department of Public Health, University of Copenhagen, Denmark
- Professor Anja Pinborg, The Fertility Clinic, Copenhagen University Hospital Rigshospitalet, Denmark
- Associate Professor Mads Kamper-Jørgensen, Section of Epidemiology, Department of Public Health, University of Copenhagen, Denmark

Assessment committee

- Professor Flemming Konradsen, Section of Global Health, Department of Public Health, University of Copenhagen, Denmark
- Professor Cecilia Ramlau-Hansen, Department of Public Health, Aarhus University, Denmark
- Dr. Siri Eldevik Håberg, Norwegian Institute of Public Health, Norway

English summary

In many countries worldwide, populations are living longer as a consequence of improved living conditions and changing disease patterns. With the increased longevity, a shift in timing of life events has taken place. People, men and women, are going through longer courses of education and the entry on the labor market happens later, as well as an increasing age of retirement. Within the shifting timeframes, also family formation has been delayed. Both first time mothers and fathers have become gradually older over the last decades, and thus the establishment of a family has become a life event that happens later in life than what was the case in earlier generations.

A higher age when attempting to achieve pregnancy is not without consequences. With increasing age it is more likely to experience difficulties with infertility; *not being able to conceive within 12 months of regular unprotected intercourse*, often due to an age-related decline in female reproductive potential. This decline, most frequently in combination with the presence of reproductive medical conditions further negatively effecting fertility such as polycystic ovarian syndrome, endometriosis, blocked tubes or low sperm quality, has consequently increased the use of medically assisted reproduction.

Some types of medically assisted reproduction require the retrieval of oocytes from the ovaries, and thus the woman must go through one or more treatment cycles with ovarian hormone stimulation. The term used to describe these treatments are assisted reproductive technology (ART) treatment. The use of hormonal stimulation has caused concern due to previous knowledge that some types of cancer are sensitive to hormones. Could the exposure to ovarian stimulation increase the risk of early death and cancer among the women treated? The aim of this thesis was to investigate the association between undergoing ART treatment with ovarian stimulation and later risk of death, ovarian cancer and breast cancer.

The study populations, the Danish National ART-Couple Cohorts (DANAC I and DANAC II), consisted of all women treated with ART in the period from 1994 to 2009, 2015 and 2016, respectively, in the three papers included. The population size gradually increased with more years included, and the number of women treated with ART increased from $n = 42,897$ in 1994-2009 to $n = 63,510$ in 1994-2016. These women were age-matched with a sample of the background population serving as untreated comparison women. Data was retrieved from the Danish health registers and population registers.

The findings in this thesis differed substantially between the three outcomes. The risk of death was lower among women undergoing ART treatment than among untreated women from the background population. This led to an investigation of the bias causing this risk to be lower, since no health-protective effect of ovarian stimulation has ever been suggested. It was concluded that women in ART treatment were characterized by the absence of life-threatening and acute disease at the time of seeking treatment, and thus there was a lower risk of death for up to ten years after initiating ART treatment, where after the risk of death was similar among women treated with ART and untreated women. The risk of ovarian cancer after undergoing ART treatment was increased, although analyses stratified by different causes of infertility showed that the increased risk was only seen among women

who had endometriosis. Women without endometriosis undergoing ART treatment had no increased risk of ovarian cancer when compared to the untreated background population, meaning that ART treatment did not appear to be an independent risk factor for ovarian cancer. The risk of breast cancer after undergoing ART treatment was also increased. Analyses stratified by age at ART treatment initiation showed that the risk increased stepwise with higher age at treatment initiation, when compared to untreated women of the same age. Particularly women initiating treatment when aged 40 years or more had an increased risk of breast cancer. No underlying cause of infertility appeared to explain this finding. A comparison between women who gave their first birth at the same age, above 40 years of age, with or without ART treatment, gave the same result. Thus, parity and higher age at first birth, known risk factors for breast cancer, did not appear to explain these findings. It is possible that ovarian stimulation during ART treatment increases the risk of breast cancer, and further studies elaborating on the characteristics of this association are warranted.

The findings in the included papers in this thesis are based on the unique Danish health registers and population registers, which provided the opportunity for data linkage on an individual level. The fact that it was possible to have a large untreated control group from the female background population and include a number of relevant confounding factors when comparing treated and untreated women is important – in many large-scale studies comparisons are conducted with samples of the background population only matched by year and age.

As the use of ART treatment increases, the assessment of risk for women associated with the treatments is important. Identification of vulnerable subgroups among the patients can provide better opportunity for clinical guidance and for relevant follow-up of patients in the future.