**Pre-selected for an award: Early ovarian ageing and long-term health consequences: Is number of oocytes harvested in ART associated to an earlier and increased risk of age-related diseases?**  
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**Study question:**

Do young women with early ovarian ageing defined as unexplained, repeatedly few oocytes harvested in ART have an increased risk of age-related diseases?

**Summary answer:**

At follow-up young women with idiopathic early ovarian ageing had an increased risk of age related diseases compared to young women with normal ovarian ageing.

**What is known already:**

Early and premature menopause is associated with an increased risk of cardiovascular diseases (CVD), osteoporosis and death. Identifying women at risk may thus allow early preventive health initiatives. Repeatedly few oocytes harvested in well stimulated assisted reproductive technology (ART) cycles is a likely predictor of advanced menopausal age when seen in young women and may thus serve as an early marker of accelerated general ageing. Oocyte harvest in ART as a measure of ovarian ageing and thus as a risk predictor of age-related morbidity and mortality has not been investigated previously.

**Study design, size, duration:**

A register-based national historical cohort study. Young women (≤ 37 years) having their first ART-treatment in a  Danish fertility clinic (public or private) during the period 1995-2014 was divided into two groups dependent on ovarian reserve status: early ovarian ageing(EOA) (n=1,234) and normal ovarian ageing(NOA) (n=18,614). Number of oocytes harvested in first and subsequent cycles was used as a marker of ovarian reserve. Several national registers were applied to assess morbidity and mortality.

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

EOA was defined as ≤ 5 oocytes in minimum two well-stimulated cycles and NOA as ≥8 oocytes in minimum 1 cycle. Known causes influencing the ovarian reserve (endometriosis, surgery, chemotherapy etc.) was reason for exclusion.  Primary outcome was overall-disease risk defined as either: CVD, osteoporosis, type-2 diabetes, cancer, all-cause death, Charlson Comorbidity index, cataract, Alzheimer’s or Parkinson’s disease or early retirement benefit. Cox regression models were used to assess the disease risk after first ART-cycle.

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

Median follow-up time from first ART-cycle to first disease event was 6.1 years (10/90 percentile 1.0/12.9) and 6.7 years( 10/90 percentile 1.0/14.1) in the EOA -and NOA group respectively.  Women with EOA had an increased risk of overall- disease when compared to women with a normal oocyte yield (Adjusted HR 1.26, 95 % CI 1.10;1.43). Stratifying on diseases categories, the EOA group had a significantly increased risk for cardiovascular diseases (adjusted HR 1.39, 95 % CI 1.15; 1.67), osteoporosis (adjusted HR 2.36, 95 % CI 1.48;3.74), Charlson comorbidity index (Adjusted HR 1.28, 95 % CI 1.06;1.54) and early retirement benefit ( adjusted HR 1.52, 95 % CI 1.06;2.19).

**Limitations, reasons for caution:**

Due to register limitations we were unable to identify the reason why no oocytes had been collected in case of cancelled cycles and we may have missed women with the most severe forms of EOA. Neither did we have information on the total doses of gonadotropin given in each cycle.

**Wider implications of the findings:**

These findings indicate that oocyte yield may serve as marker of later accelerated ageing when unexpected, repeatedly few oocytes are harvested in young women. Counselling on life-style factors as a phrophylactic effort against cardiovascular and other age related diseases may be essential for this group of women.