What is known already:

In advanced reproductive age patients, the endometrial transcriptome is associated with the age-related molecular processes that take place in the endometrium during the reproductive years. This age-related decline in endometrial receptivity is considered to be a major obstacle to conception. In vitro fertilization (IVF) using donated oocytes is a common method to overcome this limitation. In the late forties, the success rate of IVF decreases significantly, even with the implementation of embryo selection and preimplantation genetic testing. However, even with advanced maternal age (AMA) as a risk factor, the influence of the endometrial transcriptome on fertility remains unclear.

Study question:

What changes occur in the endometrium during aging and how they may affect fertility?

Summary answer:

The endometrial transcriptome of women of advanced maternal age is significantly different from the young women, indicating specific pathways involved in endometrial aging.

What is known already:

A woman’s peak reproductive years are considered to be in her twenties. The trend of postponing family planning, unfortunately, brings more women in their late forties to fertility specialists to seek for assisted conception. In vitro fertilization (IVF) using donated oocytes is a common approach to overcome the impact of maternal age on ovarian reserve. However, even with the implementation of embryo selection and preimplantation genetic testing, the IVF success rate drops significantly in the late forties. It is still unclear which age-related molecular processes take place in the endometrium and whether they may impact the ability to support embryo implantation.

Study design, size, duration:

Endometrial transcriptome profiling was done in 44 women undergoing endometrial receptivity evaluation at hormonal replacement therapy before IVF. Patients younger than 29 were considered as young maternal age group (YMA, age 23-27) and women older than 45 were considered as advanced maternal age group (AMA, age 47-50).

Participants/materials, setting, methods:

Endometrial biopsies were obtained on day 5 of progesterone treatment and RNA was extracted. All endometrial samples were evaluated for endometrial receptivity using the RefSeq database and differential expression analysis was performed using DESeq2. The study group samples (12 YMA + 12 AMA) were subject to Illumina RNA sequencing. The sequences were annotated using the RefSeq database and differential expression analysis was performed using DESeq2. We validated our results (10 YMA + 10 AMA) using quantitative-PCR and histological validation.
Main results and the role of chance: A total of 37228 mRNA transcripts were expressed in the analyzed endometrial samples. After multiple testing corrections, 144 significantly differentially expressed (DE) transcripts (92 up-regulated, 52 down-regulated) were identified in the endometrium of the AMA versus YMA group. Overexpressed genes were associated with decidu- ization (ALDH3A1), endometrial receptivity (EML5, GALNT12), cell cycle (CDKN2A) and signal transduction, while down-regulated genes included sugar metabolism and inflammation (C2CD4B, NFKB), cellular motility (SPAG6) and progesterone signaling (RPL9). The pathways most affected by age were cellular remodeling, cell motility and migration, and immune response. Interestingly, some of the identified DE genes have been previously associated with ageing. Our results suggest the involvement of p16-associated cellular senescence and the suppression of metabolic and inflammatory processes essential for endometrial preparation for embryo transfer.

Limitations, reasons for caution: The study includes only patients undergoing hormonal replacement therapy and it is unclear whether the same processes are affected by age in the natural cycles.

Wider implications of the findings: These findings allow us to explain the age-related molecular changes that take place in the endometrial tissue. Understanding these alterations and using them in assisted reproductive technology may help to improve infertility management in women with advanced reproductive age.

Trial registration number: None