Abstract title: Increased miscarriage rates following follicular-phase endometrial scratching


Study question: Does intentional endometrial injury (scratching) during the follicular phase of ovarian stimulation (OS) increase pregnancy rates in ART?

Summary answer: Pregnancy rates did not vary significantly between the endometrial injury and the control group. However, significantly higher clinical miscarriage rates were observed after endometrial injury.

What is known already: Intentional endometrial injury has been put forward as an inexpensive clinical tool capable of enhancing endometrial receptivity. However, despite its widespread use, the benefit of endometrial scratching remains controversial, with several recent randomized controlled trials (RCTs) not being able to confirm its added value. So far, most research has focused on endometrial scratching during the luteal phase of the cycle preceding the one with embryo transfer (ET), while only few studies investigated in-cycle injury during the follicular phase of OS. Also, the persistence of a scratch effect in subsequent treatment cycles remains unclear.

Study design, size, duration: This RCT included women performing IVF/ICSI in a gonadotrophin-releasing hormone antagonist supressed cycle between 2014-2018. Participants were randomized to either undergo an endometrial biopsy between day 6 to 8 of OS or to be in the control group. The primary outcome was clinical pregnancy at 7 weeks. Secondary outcomes included live birth, early pregnancy loss, procedure pain/bleeding and cumulative live birth following all ETs performed within 6 months of the study cycle.

Participants/materials, setting, methods: A total of 200 subjects (100 per study arm) were recruited, with 1 (in the control group) later withdrawing consent to participate further. In 4 patients allocated to the intervention group biopsy was impossible due to cervical stenosis or intolerable pain. The trial was stopped prematurely after an analysis in 200 of the required 360 patients. During this interim analysis, a statistically significant higher clinical miscarriage rate in the intervention group was found.

Main results and the role of chance: The study arms did not vary significantly in terms of relevant patient and IVF/ICSI cycle characteristics. The intention-to-treat clinical pregnancy rates did not vary significantly among the biopsy and the control arms (respectively, 44.0% versus 40.4%, p=0.61), nor did the live birth rates (respectively, 32.0% versus 36.4%, p=0.52). Biochemical pregnancy loss was comparable between both groups (10% in the intervention group versus 15% in the control, p=0.49), however, clinical miscarriage occurred significantly more frequent in the biopsy group (25% versus 8%, p=0.032). In the intervention group, 3% of the patients experienced procedure pain and 5% bleeding. Cumulative live birth rates taking into account all ETs performed within 6 months of the study cycle were not significantly different between the biopsy and the control group (respectively, 54.0% versus 59.6%, p=0.43).

Limitations, reasons for caution: These results are limited by the fact that the trial was stopped prior to the predetermined sample size. This, together with the pragmatic design of the study, may have limited the detection of specific
subgroups of women who may benefit from endometrial scratching.

**Wider implications of the findings:**
These findings add to the growing evidence that scratching in an unselected patient population, regardless of the period when it is done, seems to be useless. They strongly discourage intentional endometrial injury during the follicular phase of OS as it is potentially harmful. Moreover, no long-lasting benefit was found either.

**Trial registration number:**
ClinicalTrials.gov identifier NCT02061228.

**Keywords:**
IVF/ICSI
implantation
Endometrial receptivity
Miscarriage
scratching