

## Title

Asherman Syndrome after using of a levonorgestrel containing IUD, cause or coincidence?

**Background:** Asherman Syndrome is a condition characterized by the presence of hysteroscopically confirmed intrauterine adhesions and two clinical entities. First, the IUA are caused by non-intended trauma, severe infections or hypoxia of the endometrium in a gravid uterus. Second, the IUA cause clinical symptoms like menstrual abnormalities, subfertility, cyclic lower abdominal pain or recurrent pregnancy loss. The effect of levonorgestrel in a LNG-IUD is stromal decidualisation and glandular atrophy which results in a thin endometrium. The purpose of this study was to investigate if women who get pregnant quickly after removal of the LNG-IUD and undergo surgical procedure for a miscarriage are at greater risk to develop AS compared with women who used oral contraceptives.

**Methods:** We performed an observational cohort study in a university affiliated teaching hospital and referral centre for AS in The Netherlands from 2017 to 2020. We included 352 cases of women with AS who underwent hysteroscopic adhesiolysis. Adhesiolysis was performed with a Olympus 5.5 mm rigid hysteroscope with conventional instruments using fluoroscopy as a guidance method. After successful adhesiolysis an IUD without CU or hormones was placed inside the uterine cavity to prevent recurrence of adhesions. Women were treated with two consecutive cycles of hormones (estrogen and progesterone). A second look hysteroscopy was performed 8-10 weeks post-surgery.

**Results:** We identified 113 women with a first trimester procedure proceeding AS who used a LNG-IUD (n=66) or oral contraceptives (n=47). Women with AS had a higher incidence rate of LNG-IUD use than a national cohort in the Netherlands in 2019 (33% vs 10.2%). Compared with the oral contraceptives group, the LNG-IUD group were more prone to severe intrauterine adhesions (65.2% vs 36.2%, p=0.008). After adjusting for age and duration of contraceptive use, time to pregnancy within 5 months was significantly higher for women who used LNG-IUD (adjusted odds ratio, 3.776; 95% CI, 1.42-10.07; p-value 0.008).

**Conclusions:** The use of LNG-IUD was associated with increased rate of severe adhesions compared with oral contraceptives. In addition, LNG-IUD users almost all conceived within 5 months after removal of the IUD. These results suggest that LNG-IUD could be a predisposing factor for women to develop AS. One of the reasons might be a vulnerable endometrium due to a hypo estrogenic uterine environment which might women more prone to developing AS.