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PROTOCOL

Anti-adhesion Gel versus No gel following Operative Hysteroscopy prior to Subsequent fertility Treatment or timed InterCourse (AGNOHSTIC), a randomised controlled trial: protocol

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STUDY QUESTIONS: Does the application of anti-adhesion gel, compared to no gel, following operative hysteroscopy to treat intrauterine pathology in women wishing to conceive increase the chance of conception leading to live birth?

WHAT IS KNOWN ALREADY: Intrauterine adhesions (IUAs) following operative hysteroscopy may impair reproductive success in women of reproductive age. Anti-adhesion barrier gels may decrease the occurrence of IUAs, but the evidence on their effectiveness to improve reproductive outcomes is sparse and of low quality.

STUDY DESIGN, SIZE, DURATION: This multicentre, parallel group, superiority, blinded and pragmatic randomised controlled trial is being carried out in seven participating centres in Belgium. Recruitment started in April 2019. Women will be randomly allocated to treatment with anti-adhesion gel (intervention group) or no gel (control group). Sterile ultrasound gel will be applied into the vagina as a mock-procedure in both treatment arms. The patient, fertility physician and gynaecologist performing the second-look hysteroscopy are unaware of the allocated treatment. Power analysis, based on a target improvement of 15% in conception leading to live birth using anti-adhesion gel, a power of 85%, a significance level of 5%, and a drop-out rate of 10%, yielded a number of 444 patients to be randomised. The baseline rate of conception leading to live birth in the control group is expected to be 45%.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women of reproductive age (18–47 years), wishing to conceive (spontaneously or by fertility treatment) and scheduled for operative hysteroscopy to treat intrauterine pathology (endometrial polyps, myomas with uterine cavity deformation, uterine septa, IUAs or retained products of conception) are eligible for recruitment. Women may try to conceive from 3 to 6 weeks after receiving allocated treatment with follow-up ending at 30 weeks after treatment. If the woman fails to conceive within this timeframe, a second-look hysteroscopy will be scheduled within 2–6 weeks to check for IUAs. The primary endpoint is conception leading to live birth, measured at 30 weeks after randomisation. The secondary endpoints are time to conception, clinical pregnancy, miscarriage and ectopic pregnancy rates, measured at 30 weeks after receiving allocated treatment. The long-term follow-up starts when the patient is pregnant and she will be contacted every trimester.

STUDY FUNDING/COMPETING INTEREST(S): This work is funded by the Belgian Healthcare Knowledge Centre (KCE). The anti-adhesion gel is supplied at no cost by Nordic Pharma and without conditions. Dr. Tomassetti reports grants and non-financial support from Merck SA, non-financial support from Ferring SA, personal fees and non-financial support from Gedeon-Richter, outside the submitted work. None of the other authors have a conflict of interest.

Key words: operative hysteroscopy / pregnancy wish / intrauterine pathology / endometrial polyp /myoma /uterine septa / intrauterine adhesions / retained products of conception / randomised controlled trial / anti-adhesion gel

WHAT DOES THIS MEAN FOR PATIENTS?

Women wishing to conceive may suffer from abnormalities (pathologies) inside the uterus that will distort the normal cavity. These abnormalities may be, for example, polyps (or outgrowths) on the inner lining of the uterus, benign tumours that can deform the uterine cavity, intrauterine adhesions (IUAs), which are scar tissues that stick the uterine walls together, or placental and/or foetal tissue that remains in the uterus after a miscarriage, planned termination, or preterm/term delivery). The presence of these pathologies may affect women's fertility. By performing an operative hysteroscopy, which is an inspection of the uterine cavity using an endoscope introduced through the cervix, a diagnosis of intrauterine pathology can be made followed by surgical interventionto restore the womb to its normal shape.

This procedure is a keyhole surgery in which the pathology is removed through the vagina. One of the possible complications for this type of surgery is the development of scar tissue (IUAs). This complication may also affect women's fertility.

The use of an anti-adhesion gel, administered into the uterus following the operative hysteroscopy, can decrease scar tissue formation. The goal of this trial is to investigate whether the application of the anti-adhesion gel will increase the chance of a successful pregnancy. There is currently no information available on this topic, and that is what we want to investigate.

Introduction

Several intrauterine anomalies, including endometrial polyps, myomas with uterine cavity deformation, uterine septa, IUAs and retained products of conception (RPOC), have been linked with female fertility problems (Kodaman and Arici, 2007; Chan *et al.*, 2011; Bosteelset *al.*, 2018; Kliman and Frankfurter, 2019). Hysteroscopy is considered to be the gold standard to treat these intrauterine pathologies. The evidence in favour of operative hysteroscopy for improving reproductive success in women with endometrial polyps, myomas with uterine cavity deformation, uterine septa, IUAs or RPOC is sparse and of moderate to low quality. Nevertheless, hysteroscopy is very often performed, especially in women attending fertility clinics because among the medical community the presence of intrauterine pathology distorting the uterine is widely believed to impair reproductive outcome. A major long-term complication of operative hysteroscopy is the formation of IUAs (Taskin *et al.*, 2000; Hanstedeet *al.*, 2015; Hamerlynck *et al.*, 2016). The reported incidence of postsurgical IUAs at second-look hysteroscopy is 3.6% after polypectomy, 6.7% after resection of uterine septa, 31% after removal of a solitary myoma, 45% after resection of multiple myomas and 3% after removal of RPOC.

IUAs are fibrous strings at opposing walls of the uterus, developing after injury to the basal layer of the endometrium (Deans and Abbott, 2010; Salazar *et al.*, 2017). Reviews of large observational studies have demonstrated an association between IUAs and poor reproductive outcome, namely a prevalence of infertility as high as 43% and recurrent pregnancy loss in 22% (Schenker and Margalioth, 1982; Ventoliniet *al.*, 2004; Deans and Abbott, 2010). Moreover, there is an increased risk of obstetric complications after successful hysteroscopic adhesiolysis, for example abnormal placentation, preterm delivery, uterine rupture and peripartum hysterectomy (Deans *et al.*, 2018).

Women of reproductive age wishing to conceive may benefit from the IUA prevention following operative hysteroscopy. However, the optimal anti-adhesion strategy still needs to be defined because data from high quality studies on the effectiveness of anti-adhesion treatment for improving reproductive outcomes are sparse and of low quality. A Cochrane meta-analysis of five randomised controlled trials (RCTs) has demonstrated that the use of anti-adhesion gel may decrease the occurrence of IUAs at second-look hysteroscopy compared to no treatment or placebo (odds ratio (OR) 0.37, 95% CI [0.21–0.64]; $P<0.01$). The overall quality of the body of evidence retrieved was low and data on live birth rates were lacking (Acunzo *et al.*, 2003; De Iacoet *al.*, 2003; Guida *et al.*, 2004; Do *et al.*, 2005; Di Sardoet *al.*, 2011; Bosteelset *al.*, 2017).

In summary, uncertainty remains on the effectiveness of the use of anti-adhesion barrier gels following operative hysteroscopy for women wishing to conceive. In order to address this knowledge gap, our group has designed the AGNOHSTIC trial (Anti-adhesion Gel versus No gel following Operative Hysteroscopy prior to Subsequent fertility Treatment or timed InterCourse).

Outcomes

The primary endpoint of the study is conception leading to live birth, measured at 30 weeks after randomisation.

Secondary endpoints are time to conception, rates of clinical pregnancy, miscarriage and ectopic pregnancy 30 weeks after receiving allocated treatment, IUA rate and course of pregnancy.

For the definition of the reproductive outcomes we have followed the guidance of The International Committee for Monitoring Assisted Reproductive Technology (ICMART) (Zegers-Hochschild *et al.*, 2009).

Live birth is defined as the delivery of at least one live foetus after 20 completed weeks of gestation, that resulted in at least one live baby.

We will count the delivery of singleton, twin or multiple pregnancies as one live birth.

Time to pregnancy is defined as the time from receiving allocated treatment to the date of conception retrospectively determined based on the crown-rump length measurement by a first-trimester ultrasound (US).

Clinical pregnancy is defined as an US visible gestational sac. It includes ectopic pregnancy. We count multiple gestational sacs as one clinical pregnancy.

Miscarriage is defined as spontaneous loss of pregnancy before 20 completed weeks of gestation, or if gestational age is unknown, a birthweight of less than 400 gram.

Ectopic pregnancy is defined as a pregnancy in which implantation takes place outside the uterine cavity.

IUAs are measured at second-look hysteroscopy in women that failed to conceive during the follow-up period. The severity of the adhesions is scored according to the American Fertility Society (AFS) classification (Buttram*et al.*, 1988).

The course of pregnancy is registered in all women who conceive during the follow-up period, leading to a pregnancy beyond 20 weeks of gestation. Items of interest include pre-eclampsia, preterm birth, stillbirth, low/very low birthweight, caesarean section rate and neonatal complications (respiratory distress syndrome, intrapartum asphyxia, neonatal seizures, admission to the neonatal intensive care unit, congenital malformations).

Table I provides an overview of the outcome measures.

Materials and methods

Study design

The AGNOHSTIC trial is a multicentre, pragmatic, parallel group, superiority, blinded RCT.

Ethical review and trial registration

The study was approved by the central (Ghent University Hospital (670), EC/2019/0100) and local Ethical Committees of the participating centres. Written informed consent of the participants will be obtained before randomisation. The study protocol has been registered at Clinicaltrials.gov (NCT03880435, March 19, 2019).

Patient population

We will include women of reproductive age (18–47 years) wishing to conceive (spontaneously or by fertility treatment) and scheduled for operative hysteroscopy to treat intrauterine pathology (endometrial polyps, myomas with uterine cavity deformation, uterine septa, IUAs or RPOC). A CONSORT flow chart will be provided.

The mode of conception is in accordance with standard clinical practice in Belgium. Because of the pragmatic character of the trial, women will be allowed to switch from category A (spontaneous conception) to category B (fertility treatment) or switch to a different treatment within category B based on medical indications.

Intrauterine pathology will be detected by US, saline-infusion-sonography (SIS), MRI or hysterosalpingography and confirmed by diagnostic hysteroscopy according to standard clinical practice in Belgium. If in exceptional circumstances the diagnostic hysteroscopy cannot be done and/or it is very likely that pathology is present based on other imaging techniques (for example MRI), the woman will be considered eligible and operative hysteroscopy will be scheduled.

Endometrial polyps are focal endometrial outgrowths containing glands, stroma and blood vessels (Clark and Stevenson, 2017). They appear as hyperechogenic structures on US with regular contours, occupying the uterine cavity, surrounded by a small hypoechogenic halo. Colour Doppler can be used to detect the vascular stalk.

Myomas derive from myometrial cells and they may protrude into the uterine cavity (Emanuel, 2015). They are classified according to their anatomical location (PALM-COEIN classification) and in this study myomas with cavity deformation, suitable for resection by hysteroscopy, will be included (Munro *et al.*, 2011). These are submucosal myomas type 0, 1 and 2 (entirely within the uterine cavity, $<50\%$ and $\geq 50\%$ myometrial extension, respectively), and intramural myomas sufficiently large to distort the uterine cavity (hybrid myomas type 2–5) suitable for complete resection by hysteroscopy. The extent of cavity protrusion is clinically relevant for predicting the successful outcome of hysteroscopic myomectomy (Keltz *et al.*, 2015).

A uterine septum is a congenital uterine malformation. According to the ESHRE/European Society for Gynaecological Endoscopy classification system for female genital tract congenital anomalies, it is defined

Table I Overview of outcome measures in a randomised controlled trial of anti-adhesion gel versus no gel following operative hysteroscopy in women who wish to conceive.

Outcome measures	Endpoints	Time period
Primary outcome	Conception leading to live birth	At 30 weeks after randomization
Secondary outcome	Time to conception	<30 weeks after receiving treatment allocation
	Clinical pregnancy	<, >30 weeks after receiving treatment allocation
	Miscarriage	<, >30 weeks after receiving treatment allocation
	Ectopic pregnancy	<, >30 weeks after receiving treatment allocation
	Intrauterine adhesions	<, >30 weeks after receiving treatment allocation
	Course of pregnancy	>30 weeks after receiving treatment allocation
	Direct health-related costs	30 weeks after randomization

as a uterus with a normal outline and an internal indentation at the fundal midline exceeding 50% of the uterine wall thickness (Class U2) (Grimbizis et al., 2013).

IUAs, scar tissue that sticks the uterine walls together, are classified according to the AFS classification (Buttram et al., 1988).

RPOC consist of intrauterine tissue that develops after conception and persists after miscarriage, termination of pregnancy, vaginal delivery or caesarean section (Sellmyer et al., 2013).

The presence of extrauterine pathology that may affect women's fertility is allowed.

Women will be excluded if they are younger than 18 years or 48 years or older, if they have a known allergy to auto-crosslinked polysaccharide (ACP) gel or vaginal ultrasound gel, if they have an active infection of the genital tract proven by genital swabs for PCR (Chlamydia, gonorrhoea) or endometrial biopsy (endometritis), both performed if suspected based on clinical symptoms (abdominal pain, vaginal discharge or bleeding problems), if other myomas [PALM-COEIN classification type 3 and 4 intramural (entirely in the myometrium with or without endometrial contact, respectively), types 5–7 subserosal (protruding towards the abdominal cavity with $<$, $\geq$ 50% myometrial extension or pedunculated, respectively) and type 8 other (cervical, parasitic)] are present as the sole uterine pathology, if different types of intrauterine pathology are present preoperatively, if they have no pregnancy wish, and if they already have participated in the trial.

Recruitment procedure

Women attending Belgian hospitals, fulfilling the inclusion criteria will be invited to take part in the study. Initially, recruitment was started in six centres (Ghent University Hospital, University Hospital Brussels, University Hospital Leuven, Cliniques Universitaires Saint-Luc Brussels, Centre HospitalierUniversitaire Liège and Imelda Hospital Bonheiden). To speed up the recruitment, an additional centre (Jessa Hospital Hasselt) joined the group in 2020.

Recruitment started in April 2019 and is ongoing. The planned study period will be 4.5 years.

Randomisation

All eligible women who provided written informed consent will be randomised from 1 day up to 1 hour before the operative hysteroscopy. The study is a parallel-group RCT with a 1:1 allocation ratio and stratified randomisation with computer generated random permuted blocks of variable sizes to avoid that the surgeon may predict the treatment allocation.

The stratification factors are centre(seven categories) and type of pathology treated by hysteroscopy (five categories).

Study drug

The intervention under study is the application of an anti-adhesion gel, namely Hyalobarrier® gel endo (Nordic Pharma), after the complete removal of intrauterine pathology (endometrial polyps, myomas with uterine cavity deformation, uterine septa, IUAs or RPOC) by hysteroscopy. A second operation will be planned in case of incomplete pathology removal. The anti-adhesion gel is sterile, transparent and highly viscous, and made from ACP obtained by condensation of hyaluronic acid. Due to its viscosity, it keeps the surrounding tissue separate during the recovery period after surgery. Seven days after application in the uterine cavity, the gel is fully absorbed (Renier et al., 2005). In the uterine cavity it is shown to remain *in situ* for at least 72 hours (Acunzo et al., 2003). Yang et al.(2013) showed a different endometrial healing process for various hysteroscopic procedures.The shortest time period occurred after polypectomy (1–2 months), and the longest time period was seen after myomectomy. Whether the time frame of 72 hours is sufficient remains to be seen. The effectiveness of Hyalobarrier® gel has been demonstrated during surgical procedures in the abdomen and pelvis during clinical studies(De Iacoet al., 2001; Acunzo et al., 2003; Pellicano et al., 2003, 2005; Pucciarelli et al., 2003; Guida et al., 2004; Mais et al., 2006, 2012; Metwally et al., 2007). It is indicated for use in laparoscopic and hysteroscopic procedures and is available as a single-use disposable syringe. Each syringe contains 10 ml of sterile gel containing 30 mg of ACP per ml. For administration, individually packaged cannulas of 30 cm length are enclosed. All reportable adverse events will be recorded in the patient's file and in the electronic Case Report Form (e-CRF) between randomisation and the last trial related activity. Medical events that occur between signing of the Informed consent and the randomisation will be documented on the medical and surgical history section and concomitant diseases page of the e-CRF. Additionally, all Serious Adverse Device Effects (SADE), Unanticipated Serious Adverse Device Effects (USADE), incidents and other significant safety issues will be reported immediately but no later than 3 calendar days after investigational site study personnel's awareness of the event to the sponsor and chief investigator. A detailed listing of our safety reporting is shown in Supplementary File S1.

No gel will be applied in the uterine cavity of women assigned to the control group.

The patient, fertility physician and gynaecologist performing the second-look hysteroscopy will be unaware of the allocated treatment. To ensure blinding, and to rule out a treatment effect of placebo gel applied in the uterine cavity, sterile US gel will be applied into the vagina in both treatment arms. The surgeons doing the operative hysteroscopy cannot be blinded. If the fertility physician or the gynaecologist doing the second-look hysteroscopy has also performed the operative hysteroscopy, blinding will be assured by notification of treatment allocation to another caretaker (colleague gynaecologist or resident) after the surgeon has left the operating room. The gel will subsequently be applied by this caretaker. The biostatistician and the study nurses were blinded and did not make any decisions with respect to the further treatment and/or follow-up of the study participants.

Co-treatment with hormonal medication may be given or repeated SIS or hysteroscopy may be scheduled for severe IUAs, according to the standard practice of the participating centre. This decision should be made before the notification of the treatment allocation.

Follow-up

The trial flow chart is shown in Fig. 1. According to local practice, 3–6 weeks after the operative hysteroscopy with complete pathology removal, women will be scheduled for a postoperative visit (telephone or physical) or a second-look hysteroscopy. Subsequently, they may start trying to conceive by regular sexual intercourse or fertility treatment (4–6 cycles ovulation induction, 4–6 cycles controlled ovarian

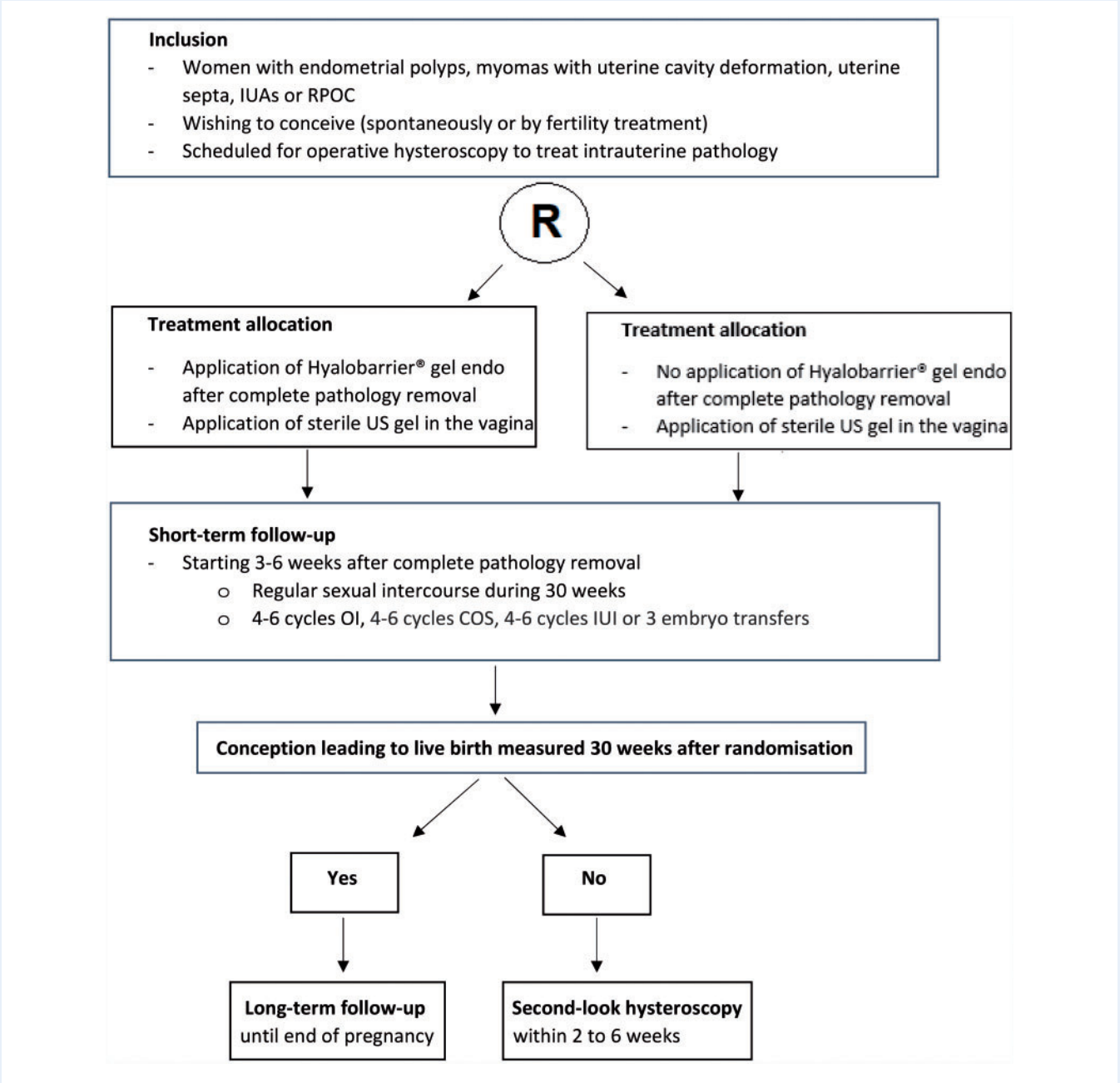

Figure 1. Trial flow chart for a randomised controlled trial of anti-adhesion gel versus no gel following operative hysteroscopy in women who wish to conceive.IUAs, intrauterine adhesions; RPOC, retained products of conception; OI, ovulation induction;COS, controlled ovarian stimulation; US, ultrasound.

stimulation or 4–6 cycles IUI or 3 embryo transfers). Women will be contacted every month to check if they are pregnant.

The short-term follow-up ends 30 weeks after randomisation for the primary endpoint. This is in concordance with the CONSORT guidelines (Moher *et al.*, 2010). Secondary endpoints, namely time to conception and rates of clinical pregnancy, miscarriage and ectopic pregnancy, are measured 30 weeks after receiving allocated treatment. In all women that fail to conceive within this timeframe, a second-look hysteroscopy will be scheduled within 2–6 weeks to check for IUAs.

The long-term follow-up starts if the patient is pregnant, within 30 weeks after receiving allocated treatment. Women will be contacted every trimester.

An overview of the collected data is shown in Supplementary Files S2–S10.

Statistical analysis

Continuous variables will be summarised with descriptive statistics (mean and SD for data that are approximately normally distributed

and median and interquartile range otherwise). Categorical data will be presented as frequency and percentage.

The primary endpoint, conception leading to live birth 30 weeks after randomisation, will be analysed using binary logistic regression taking centre and type of pathology into account. The estimated OR with 95% CI will be reported.

The secondary endpoint, time to conception, will be analysed using Kaplan–Meier analyses and randomisation groups will be compared using a Cox model adjusting for centre and type of pathology. The intervention effect will be expressed as a hazard ratio.

The secondary endpoints, clinical pregnancy, miscarriage, ectopic pregnancy and IUA rates, will be analysed similarly as the primary endpoint. However, the variables describing the course of pregnancy will be expressed as OR or mean difference.

The primary analysis will be the intention-to-treat analysis (ITT) analysis. All participants will be included in the analysis in the groups to which they were originally assigned, regardless of what subsequently occurred. Multivariate imputation by fully conditional specificationwill be used for outcome data that are missing (Moher *et al.*, 2010). The predictors used for the imputation model will be randomisation group, centre, intended mode of fertility treatment, change in fertility treatment (yes/no), type of pathology treated by operative hysteroscopy, age of the participant, weight and height of the participant, duration of infertility, type of infertility (primary or secondary), cause of infertility (ovulatory disorder, male factor, tubal factor, unexplained, endometriosis) and smoking (yes/no).

Two sensitivity analyses will be performed. First, ITT with non-response imputation. Second, a per protocol analysis, excluding all women in the ITT population who no longer wish to conceive, who have an incomplete follow-up or who received a treatment different from the randomised group.

Two subgroup analyses will be performed. First, to explore whether the effect of ACP gel on the primary endpoint might differ between types of pathology. This analysis is similar to that of the primary endpoint and a stratification factor 'type of pathology treated by hysteroscopy' will be added as a categorical predictor variable. An interaction term between type of pathology and randomisation group will be included in the model. Second, two scenarios are considered: no change in fertility treatment and change in fertility treatment. These analyses are similar to that of the primary endpoint. All subgroup analyses will be performed both on the ITT and the protocol-compliant sample.

Statistical analyses will be performed with the use of SAS (SAS Institute, Cary, NC, USA) and R (R Core Team, 2019).

Sample size

Sample size calculation for the logistic regression on the primary endpoint was performed in SAS version 9.4 using the power procedure. The alternative hypothesis states that the proportion of pregnancies leading to live birth at 30 weeks after randomisation is 45% in the control group (no ACP gel) and 60% in the intervention group (ACP gel).

The sample size analysis was based upon our own database regarding the pregnancy rate after operative hysteroscopy performed from 2011 until 2016. Based on these data, a pregnancy rate of 45% was expected in the control group. The pregnancy rate for the intervention group was expected to be 60%. This percentage is based on expert opinion in combination with the pregnancy rate seen in a subgroup of single/lesbian women and male infertility in the same database.

Based upon the Belgian Register for Assisted Procreation (BELRAP database), the cumulative clinical pregnancy rate after six IUIs and three embryo transfers was 47% and 46.5%, respectively, regardless of age.

We need 399 participants to achieve 85% power at a significance level of 5%, to demonstrate or refute an increase from 45% to 60%. We expect a drop-out rate of a maximum 10% after randomisation, leading to a sample size of 444 participants that should be randomised.

Sample size analysis per pathology was not performed because of the pragmatic design.

Discussion

Operative hysteroscopy to treat intrauterine pathologies is a frequently performed procedure in women wishing to conceive. Following the procedure, IUAs may develop and this may compromise women's fertility prognosis.

A Cochrane systematic review on the effectiveness of anti-adhesion methods following operative hysteroscopy in women wishing to conceive, to improve key reproductive outcomes or to decrease IUAs has shown that the quality of evidence was low (Bosteelset *al.*, 2017).

The Prevention of Adhesions Post Abortion (PAPA) trial is the largest multicentre RCT comparing the application of ACP gel after dilation and curettage (D&C) for miscarriage with no treatment in a population at risk for IUAs (defined as at least one D&C in the history) (Hooker *et al.*, 2017). The IUA rate was significantly lower in the ACP group compared to the control group. Moreover, the mean adhesion score and the amount of moderate to severe IUAs, assessed by the AFS scoring system, were significantly lower after the application of ACP gel. Thus, ACP gel may be of benefit in a specific subgroup of women scheduled for D&C for miscarriage with at least one D&C in the history.

The authors have recently reported the long-term follow-up, including fertility and obstetric outcomes, of the women who participated in the PAPA trial (Hooker *et al.*, 2018). Questionnaires were sent 3, 6 and 12 months after D&C. The rates of pregnancy, miscarriage and live birth, and time to conception were not statistically different. However, the PAPA trial has some important limitations. First, the study was not powered for reproductive outcomes. Second, second-look hysteroscopy revealed more IUAs in the control group, and these were removed because it was considered to be unethical not to perform hysteroscopic adhesiolysis.

Currently, in Belgium, anti-adhesion gels are only partially reimbursed in specific conditions (<40 years old, wishing to conceive, scheduled for laparoscopy or laparotomy) and there is no reimbursement for the use in hysteroscopy.

The AGNOHSTIC trial aims to provide the evidence that a decrease in IUA formation by application of ACP gel following operative hysteroscopy, improves reproductive outcomes in women wishing to conceive. If the AGNOHSTIC trial succeeds, we plan to perform a health-economic analysis in order to emphasize the need for reimbursement. This will be the topic of a separate publication.

This study has some important strengths. To our knowledge, this is the first large multicentre and well-designed RCT focusing on the influence of ACP gel on reproductive outcomes. Our study is powered to

detect a difference in the primary study outcome, conception leading to live birth, measured at a fixed time point, namely 30 weeks after randomisation. Measuring 'live birth' as primary endpoint would imply a longer follow-up period and a risk of multiple outcomes in one patient, different modes of conception per patient and risk of drop-out. It would make the design of this pragmatic trial more complicated.

Moreover, women will be well monitored during the short-term follow-up by monthly contact and every trimester during long-term follow-up instead of using questionnaires, which may be accompanied by recall bias.

Furthermore, patient representatives are involved and report to the trial steering committee.

This study also has some limitations. Our study population will be a mix of women trying to conceive by regular sexual intercourse or fertility treatment. This composition was chosen because of the pragmatic character of our study, to meet the recruitment options of all the involved centres, and to reach our large sample size in an acceptable time period.

Women will be included until the age of 47 years and it is known that age is an important predictor for fertility. The present study uses the stratified randomization method. However, age is not included as a covariate: this is a pragmatic study and the Belgian law allows transfer of frozen embryos until 47 years. The 'bottom line' of the trial is to study whether the application of ACP gel subsequent to operative hysteroscopy in women wishing to conceive improves their reproductive outcome. Co-treatment with hormonal medication may be given or repeated SIS or hysteroscopy may be scheduled for severe IUAs, according to the standard practice of the participating centre. Thus, we avoid the possibility that women with severe IUAs allocated to the control group do not receive a postoperative anti-adhesion treatment.

At 3–6 weeks after the operative hysteroscopy with complete pathology removal, women may be scheduled for second-look hysteroscopy, according to local practices. IUAs on second-look hysteroscopy will be treated by adhesiolysis. This may impact the primary outcome in favour of the control group. However, both issues, namely additional anti-adhesion treatment and adhesiolysis, will be solved because stratification is performed per centre and pathology.

Lastly, to be in line with the CONSORT guidelines, the primary endpoint will be measured at a pre-specified time point, namely 30 weeks after randomisation. Only if the intrauterine pathology is completely removed, the allocated treatment will be announced and applied. Otherwise, women are scheduled for a second operative hysteroscopy followed by the allocated treatment. Thus, their timeframe to become pregnant will be shorter.

Acknowledgements

We are very grateful to the participating women. We would also like to thank all clinical investigators and research nurses in the participating centres for their effort. We appreciate the commitment of two patient representatives and two independent experts to attend the trial steering committee meetings.

Authors' roles

JB and SW have developed the first version of the protocol. SvW and TH further edited the protocol. JB, SW and SvW were responsible for the logistical aspects of the start of the trial. SvW is currently responsible for the logistical aspects of the trial. SvW has drafted the first version of the paper. JB, SW and TH further edited the paper. All authors managed the trial in the different hospitals and commented on the paper. All authors read and approved the final paper.

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Conflict of interest

Dr. Tomassetti reports grants and non-financial support from Merck SA, non-financial support from Ferring SA, personal fees and non-financial support from Gedeon-Richter, outside the submitted work.

The other authors have no conflict of interest.

References

Acunzo G, Guida M, Pellicano M, Tommaselli GA, Sardo DiSA, Bifulco G, Cirillo D, Taylor A, Nappi C. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Hum Reprod* 2003;**18**:1918–1921.

BosteelsJ, Wessel S van, WeyersS, BroekmanF, D'Hooghe T, Bongers M, MolB. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database Syst Rev* 2018;**12**:CD009461.doi: 10.1002/14651858.CD009461.pub4.

BosteelsJ, WeyersS, D'Hooghe TM, Torrance H, BroekmansFJ, Chua SJ, MolBWJ. Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility.*Cochrane Database Syst Rev*2017;**11**:CD011110.doi: 10.1002/14651858.CD011110.pub3.

ButtramVC, Gomel V, SieglerA, DeCherneyA, Gibbons W, MarchC. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. *Fertil Steril*1988;**49**:944–955.

Clark TJ, Stevenson H. Endometrial Polyps and Abnormal Uterine Bleeding (AUB-P): what is the relationship, how are they diagnosed and how are they treated?*Best Pract Res Clin Obstet Gynaecol* 2017; **40**:89–104.

Deans R, Abbott J. Review of intrauterine adhesions.*J Minim Invasive Gynecol* 2010;**17**:555–569.

Deans R, VancaillieT, Ledger W, Liu J, Abbott JA.Live birth rate and obstetric complications following the hysteroscopic management of intrauterine adhesions including Asherman syndrome.*Hum Reprod* 2018;**33**:1847–1853.

Di Sardo SA, SpinelliM, Bramante S, ScognamiglioM, Greco E, Guida M, CelaV, Nappi C. Efficacy of a polyethylene oxide-sodium carboxymethylcellulose gel in prevention of intrauterine adhesions after hysteroscopic surgery.*J Minim Invasive Gynecol* 2011;**18**: 462–469.

Do JW, Lee YW, Park HJ, Park YS.The effectiveness of hyaluronic acid + sodium carboxymethyl cellulose in the prevention of

intrauterine adhesion after intrauterine surgery.*J. Korean Gynecol Endoscopy Minimally Invasive Surg*2005;**17**:112–117.

Emanuel MH.Hysteroscopy and the treatment of uterine fibroids.*Best Pract Res Clin Obstet Gynaecol* 2015;**29**:920–929.

Guida M, Acunzo G, Spiezio Sardo A, DiBifulco G, Piccoli R, Pellicano M, Cerrota G, Cirillo D, Nappi C. Effectiveness of autocrosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. *Hum Reprod* 2004;**19**:1461–1464.

Hamerlynck TWO, Vliet HAAM, VanBeerens A-S, WeyersS, Schoot BC. Hysteroscopic morcellation versus loop resection for removal of placental remnants: a randomized trial. *J Minim Invasive Gynecol* 2016;**23**:1172–1180.

HanstedeMMF, MeijE, Van DerGoedemans L, Emanuel MH.Results of centralized Asherman surgery, 2003-2013.*Fertil Steril* 2015;**104**: 1561–1568.e1.

Hooker AB, Leeuw R, deVen PM, van deBakkum EA, Thurkow AL, Vogel NEA, Vliet HAAM, vanBongers MY, Emanuel MH, Verdonkschot AEM*et al*. Prevalence of intrauterine adhesions after the application of hyaluronic acid gel after dilatation and curettage in women with at least one previous curettage: short-term outcomes of a multicenter, prospective randomized controlled trial. *Fertil Steril* 2017;**107**:1223–1231.e3.

Hooker AB, Leeuw RA, deVen PM, van deBrölmann HAM, Huirne JAF.Reproductive performance after the application of hyaluronic acid gel after dilation and curettage in women who have experienced at least one previous curettage: long-term results of a multicenter prospective randomized trial. *Fertil Steril* 2018;**110**: 1231–1238.

Iaco PA, DeMuzzupapa G, Bovicelli A, Marconi S, Bitti SR, Sansovini M, Bovicelli L. Hyaluronan derivative gel (HYALOBARRIER(r) gel) in intrauterine adhesion (IUA) prevention after operative hysteroscopy. *Ellipse* 2003;15–18.

Keltz MD, Greene AD, Morrissey MB, Vega M, Moshier E. Sonohysterographic predictors of successful hysteroscopic myomectomies. *J Soc Laparoendosc Surg* 2015;**19**:e2014.00105.

Kliman HJ, Frankfurter D. Clinical approach to recurrent implantation failure: evidence-based evaluation of the endometrium. *Fertil Steril* 2019;**111**:618–628.

Kodaman PH, Arici A. Intra-uterine adhesions and fertility outcome: How to optimize success?*Curr Opin Obstet Gynecol* 2007;**19**:207–214.

Mais V, Bracco GL, Litta P, Gargiulo T, Melis GB.Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study. *Hum Reprod* 2006;**21**:1248–1254.

Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of auto-crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: a systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* 2012;**160**:1–5. Elsevier Ireland Ltd.

Metwally M, Gorvy D, Watson A, Li TC.Hyaluronic acid fluid agents for the prevention of adhesions after fertility-preserving gynecological surgery: a meta-analysis of randomized controlled trials. *Fertil Steril* 2007;**87**:1139–1146.

Munro MG, Critchley HOD, Fraser IS.The FIGO classification of causes of abnormal uterine bleeding in the reproductive years.*Fertil Steril* 2011;**95**:2204–2208.e3.

Pellicano M, Bramante S, Cirillo D, Palomba S, Bifulco G, Zullo F, Nappi C. Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: aprospective, randomized, controlled study. *Fertil Steril* 2003;**80**:441–444.

Pellicano M, Guida M, Bramante S, Acunzo G, Sardo ADS, Tommaselli GA, Nappi C. Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy.*Fertil Steril* 2005;**83**: 498–500.

Salazar CA, Isaacson K, Morris S.A comprehensive review of Asherman's syndrome: causes, symptoms and treatment options. *Curr Opin Obstet Gynecol* 2017;**29**:249–256.

Schenker JG, Margalioth EJ.Intrauterine adhesions: an updated appraisal.*Internet*1982;**37**:593–610.

Sellmyer MA, Desser TS, Maturen KE, Jeffrey RB, Kamaya A. Physiologic, histologic, and imaging features of retained products of conception. *RadioGraphics [Internet]*2013;**33**:781–796.

Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, Wheeler JM. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery.*J Am Assoc Gynecol Laparosc* 2000;**7**:351–354.

Yang JH, Chen MJ, Chen C, DerChen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries.*Fertil Steril* 2013;**99**:2092–2096.e3. Elsevier Inc.

Zegers-Hochschild F, Adamson GD, J DeM, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. *Res Train Hum Reprod World Heal Organ* 2009;**2009**:92: 1520–1524.

Chan YY, Jayaprakasan K, Tan A, Thornton JG, Coomarasamy A, Raine-Fenning NJ. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. *Ultrasound Obstet Gynecol* 2011;**38**:371–382.

Grimbizis GF, Gordts S, Spiezio Sardo A, DiBrucker S, Angelis C, DeGergolet M, Li T-C, Tanos V, Brölmann H, Gianaroli L*et al*. The ESHRE-ESGE consensus on the classification of female genital tract congenital anomalies.*Gynecol Surg*2013;**10**:199–212.

Iaco PA, DeMuzzupapa G, Bigon E, Pressato D, Donà M, Pavesio A, Bovicelli L. Efficacy of a hyaluronan derivative gel in postsurgical adhesion prevention in the presence of inadequate hemostasis. *Surgery* 2001;**130**:60–64.

Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869–c869.

Pucciarelli S, Codello L, Rosato A, Bianco P, DelVecchiato G, Lise M. Effect of antiadhesive agents on peritoneal carcinomatosis in an experimental model. *Br J Surg* 2003;**90**:66–71.

Renier D, Bellato P, Bellini D, Pavesio A, Pressato D, Borrione A. Pharmacokinetic behaviour of ACP gel, an autocrosslinked hyaluronan derivative, after intraperitoneal administration.*Biomaterials* 2005;**26**:5368–5374.

VentoliniG, Zhang M, Gruber J. Hysteroscopy in the evaluation of patients with recurrent pregnancy loss: a cohort study in a primary care population. *Surg Endosc*2004;**18**:1782–1784.