LIMITATIONS, REASON FOR CAUTION: The sample was large and nationally representative. Response rate was in line with other survey studies but possibly more distressed women were less likely to respond. Extensive treatment data were available, but retrospectively self-reported and could be subject to memory bias.

WIDER IMPLICATIONS OF THE FINDINGS: Patients that start treatment earlier and do more recommended IVF cycles adjust better. Those who do not abandon their wish experience several adjustment difficulties. Professionals can prepare patients for the grief associated with unsuccessful infertility treatment. Patients at risk for maladjustment could be identified via assessment of their possibilities to re-focus their lives. They could receive additional support to pursue new life-goals (increased work dedication seems adaptive) and/or be advised to seek group/individual support.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by a grant from the Dutch Cancer Society (2006-3631). No competing interests exist. Trial registration number N/A

SELECTED ORAL COMMUNICATION SESSION
Session 45: Clinical female infertility
Tuesday 9 July 2013 15:15 - 16:30

O-171 An economic analysis comparing IVF with a single embryo transfer and IVF with a modified natural cycle to IUI with hyperstimulation (the INeS trial)
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Study question: In couples with unexplained or mild male subfertility and low fertility prospects, are 3 cycles of in vitro fertilization with a single embryo transfer (IVF-SET) or 6 cycles of IVF with a modified natural cycle (IVF-MNC) more cost-effective compared to 6 cycles of intra-uterine insemination with controlled ovarian hyperstimulation (IUI-COH)?

Summary answer: Preliminary results suggest that in couples with unfavorable fertility prospects and unexplained or mild male subfertility, IVF-SET and IVF-MNC are not cost-effective alternatives compared to IUI-COH.

What is known already: In couples with unfavorable fertility prospects and unexplained or mild male subfertility Dutch guidelines recommend six cycles of IUI-COH as the treatment of first choice. IUI-COH is associated with high multiple pregnancy rates (approximately 10%). IVF-SET and IVF-MNC are alternative fertility treatments and are associated with lower multiple pregnancy rates. Multiple pregnancies imply high costs due to perinatal complications. At present, these techniques have not been assessed in direct randomized comparisons.

Study design, size, duration: We performed a cost-effectiveness analysis, based on the INeS trial (randomized controlled trial). Between January 2009 and February 2011 605 couples were allocated to three cycles of IVF SET (including frozen embryo transfers), six cycles of IVF-MNC or six cycles IUI-COH. Follow up period was 12 months.

Participants/materials, setting, methods: Direct medical costs (treatment procedures and medication) were based on tariffs of the Dutch Health Insurance Board. Indirect costs could not yet be ascertained. We report on ongoing pregnancy as the primary outcome, birth of a healthy singleton, was not yet available. All analyses were by intention to treat.

Main results and the role of chance: We randomly allocated 605 couples to IVF-SET (N = 203), IVF-MNC (N = 195) or IUI-COH (N = 207). These preliminary results are based on collected data of 586 couples; complete follow-up was not yet available. Ongoing pregnancy rates (singleton and multiple) were 57% after IVF-SET, 49% after IVF-MNC and 54% after IUI-COH. Mean direct medical costs per patient were €3.270 for IVF-SET, €4.787 for IVF-MNC and €2.108 for IUI-COH. Direct medical costs per ongoing pregnancy were €5.723 for IVF-SET, €9.838 for IVF-MNC and €3.925 for IUI-COH. Incremental cost-effectiveness ratio (ICER) for IVF-SET compared to IUI-COH was €58.756 per patient for an additional ongoing pregnancy. In the comparison of IVF-MNC to IUI-COH, the latter was the dominant strategy (more ongoing pregnancies for lower costs).

Limitations, reason for caution: These preliminary results are based on direct medical costs until an ongoing pregnancy. Costs due to multiple pregnancies did not play a role as yet. Sensitivity analyses will be required to evaluate the impact of differences in resource use and costs.

WIDER IMPLICATIONS OF THE FINDINGS: These preliminary results suggest that IVF-SET and IVF-MNC are less cost-effective than IUI-COH until ongoing pregnancy. The perinatal costs, e.g. of multiple pregnancies, will play a larger role when looking at our primary outcome birth of a healthy singleton. These results will determine which treatment will be the treatment of first choice in couples with unexplained or mild male subfertility and low fertility prospects.

Study funding/competing interests: The study was supported by a grant from ZonMW, the Netherlands Organization for Health Research and Development, and a grant from Zorgverzekeraars Nederland, the Netherlands association of health care insurers.

Trial registration number: The trial was registered at the Dutch trial registry (NTR 939).

O-172 Effect of controlled ovarian stimulation with low dose human menopausal gonadotrophin or clomiphene on reproductive outcome after intrauterine insemination: a prospective, multicenter randomized trial
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Study question: The aim of the study was to test the hypothesis that the pregnancy rate per cycle after intrauterine insemination (IUI) cycle is significantly higher after Controlled Ovarian stimulation (COS) with low dose human menopausal gonadotrophins (HMG COS) than after COS with clomiphene citrate (CC COS).

Summary answer: Clinical pregnancy rate with positive fetal heart beat (FHB + pregnancies) and live birth delivery rate (LBR) after treatment with IUI was significantly higher after HMG COS than after CC COS, whereas the multiple pregnancy rates were low, and the cancellation rate per started IUI cycle was lower after HMG COS.

What is known already: There is sufficient evidence that intrauterine insemination combined with COS is an efficient treatment for mild male subfertility, unexplained subfertility and minimal-mild endometriosis. Although current evidence suggests that reproductive outcome after IUI is higher after HMG COS than after CC COS (Cantinieu et al., 2007), more randomized trials with sufficient power are needed, also with respect to a possibly increased multiple pregnancy rate after HMG COS than after CC OS.

Study design, size, duration: 620 IUI cycles in 306 patients were randomized to HMG COS (n = 322) or to CC COS (n = 298). To detect an absolute difference of 10 % in ‘clinical pregnancy with positive fetal heart beat’, 219 cycles were needed in each group at a statistical power of 0.80.

Participants/materials, setting, methods: 306 patients undergoing IUI treatment (2004-2011) and fulfilling the inclusion criteria (failure to conceive for ≥ 12 months, female age < 42 years, at least one patent Fallopian tube, total motility count (TMC) ≥ 5.0 million spermatozoa after capacitation, informed consent) were randomized.

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Main results and the role of chance: Both groups were comparable with respect to female age, BMI, basal FSH, mean cycle duration, TMC, indication, type of infertility and tubal patency. When compared to CC cycles, HMG cycles had a lower number of follicles at time of HCG administration (hMG 1.2 vs. CC 1.5, \( p < .0001 \)), increased endometrial thickness (hMG 8.5 mm vs. CC 7.5 mm, \( p < .0001 \)), higher FHB + pregnancy rate (HMG 40/322 (12%) vs. CC group 20/298 (7%), \( p = 0.02 \)), higher LBR (HMG 38/322 (12%) vs. CC 19/298 (6%), \( p = 0.02 \), and similar multiple pregnancy rate (HMG 3/40 (8%) vs. CC 1/20 (5%), \( p = 0.7144 \)), and a lower cancellation rate per started cycle (\( p < .001 \), HMG 15/322 (4.7%) versus CC 46/298 (15.4%), but reasons for cancellation were comparable between groups.

Limitations, reason for caution: Since cycles, not patients were randomized, statistical analysis controlled for presence of multiple measures. Linear mixed models were used for continuous measures. For binary outcomes we estimated the relative risk using a Poisson model with log link and using generalized estimating equations.

Wider implications of the findings: In this study, the largest RCT comparing low dose HMG COS with CC COS for IUI, better reproductive outcome (higher rate of FHB + pregnancies and LBR, low multiple pregnancy rate) and lower cancellation rate per started cycle was observed after HMG COS. A health economic analysis of our data is planned to test the hypothesis that low dose HMG COS before IUI is associated with increased cost-effectiveness when compared to CC COS.

Study funding/competing interest(s): The authors have to declare.

Trial registration number: NCT01569945

O-173 The impact of Uterine Artery Embolization (UAE) on subsequent fertility when used as a substitute for invasive operations like myomectomy and in obstetrical emergencies

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Study question: What will be the follow up of patients regarding their reproductive outcome and menstrual cyclicity after Uterine Artery Embolization?

Summary answer: Uterine Artery Embolization does not have any effect on ovarian function in younger women, a finding which is of a particular importance to women who wish to retain their fertility after embolization. Uterine artery embolization is a safe procedure for women who want to preserve their fertility.

What is known already: BJOG 2010 Jul; 117(8):985-9
There was no evidence for Uterine Artery Embolization accelerating a deterioration of ovarian function up to 1 year after treatment when compared with surgery. BJOG 2007 Nov 14(11):1340-51
27 women who had Uterine Artery Embolization reported 37 pregnancies after treatment resulting in 19 live births.

Study design, size, duration: 76 patients of intractable haemorrhage and 16 patients of fibroids were followed up after Uterine Artery Embolization regarding their menstrual cyclicity and reproductive outcome. UAE was done using polyvinyl alcohol particles which blocked the uterine artery. In two cases UAE was done prior to laparoscopic myomectomy for huge fibroids. Angiographic embolization has been used as a fertility preserving method to control intractable life threatening pelvic hemorrhage. Normal menstruation resumed in 80% patients within three months. Eight patients resumed menstruation within a year. Seven patients conceived within a year and one patient had twins.

Participants/materials, setting, methods: Vascular access is achieved from both femoral arteries and cannulation of internal iliac artery done. The site of origin of uterine artery is located by using hand injection in AP and Oblique views. Confirmation of uterine artery is done by looking at its tortuousity, course and blush. Materials used to block the uterine artery included coils, PVA particles (500-750 mg) and gel foam. A total of 16 patients for fibroids and 76 patients for intractable haemorrhage were taken up for the procedure. These included haemodynamically unstable patients, post vaginal delivery haemorrhage, post abortion haemorrhage, patients of thrombocytopenia with PPH (because of dengue fever), post LSCS haemorrhage, pseudoaneurysm and fibroids.

Normal menstruation resumed in 80% patients within three months. Four patients resumed menstruation within a year. Three patients conceived within a year, one patient had twins.

Main results and the role of chance: A total of 16 patients for fibroids and 76 patients for intractable haemorrhage were taken up for the procedure. These included haemodynamically unstable patients, post vaginal delivery haemorrhage, post abortion haemorrhage, patients of thrombocytopenia with PPH (because of dengue fever), post LSCS haemorrhage, pseudoaneurysm and fibroids.

Normal menstruation resumed in 80% patients within three months. Eight patients resumed menstruation within a year. Seven patients conceived within a year and one patient had twins.

Limitations, reason for caution: Within 30 days. Post embolization syndrome consisting of pain, nausea, fever, flu like symptom with raised inflammatory marker and leucocyte counts.

Late-beyond 30 days
(1) Vaginal discharge in 16% at 12 months
(2) Fibroid expulsion in 10% and is more frequent with submucosal fibroid
(3) Amenorrhea - UAE can interfere temporarily with ovarian blood supply.

Wider implications of the findings: According to case reports and literature the average fibroid shrinkage is very variable but may be as much as 60% at 6 months which is maintained in the longer term with further shrinkage up to 1 year.

UAE can serve as a substitute for invasive operations such as hysterectomy and myomectomy.

Study funding/competing interest(s): N/A

Trial registration number: N/A

O-174 Clinical predictive criteria for live birth following elective single embryo transfer

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Study question: We aimed to define clinical criteria from the patients related to the occurrence of live birth in case of elective Single Embryo Transfer (eSET).

Summary answer: This study showed that Body Mass Index (BMI) appears to be the only clinical parameter statistically associated with delivery following eSET strategy in a good prognosis infertile population.

What is known already: eSET strategy during in vitro fertilization treatments (IVF) is known to reduce significantly the multiple pregnancy rate (PR) with no change concerning the cumulative PR when compared with double embryo transfer (DET). We recently confirmed these results proposing prospectively eSET or DET in a selected infertile population of good prognosis. So far, only one study evaluated clinical predictive factors for live birth following eSET.

Study design, size, duration: We analysed retrospectively 409 eSET at day 2/3 between March 2005 and July 2012, proposed in case of (i) woman’s age < 37 years, (ii) first/second IVF cycle, (iii) > 2 good quality embryos obtained (3-5-10 blastomeres at day 2/3 and <20% fragmentation), including one top embryo (4/8 cells).

Participants/materials, setting, methods: In total, 124/409 live births (30.3%) were obtained, separating patients into groups of women who had birth or not. Different clinical parameters of interest in this study were compared between groups, considering statistical tests at \( p < 0.05 \) significance level.

Main results and the role of chance: We observed no significant difference between each group, concerning women and men’s age, indication and length of infertility, IVF rank, FSH and estradiol levels, antral follicle count, measured at day 3 of a spontaneous cycle, amount of FSH dose administered during the stimulation protocol, estradiol, progesterone concentrations and endometrial thickness at day of hCG injection. By comparing BMI between the two groups, we report a statistically higher average BMI among women who did not deliver (24.637 kg/m\(^2\)) compared with those who did (23.375 kg/m\(^2\); \( p = 0.014 \)). In addition, the analysis of cigarette smoking shows no significative difference but a trend in favour of smoking in the group of women who delivered following eSET (\( p = 0.074 \)).

Limitations, reason for caution: Implication of cigarette consumption and BMI on live birth rate following eSET should be made clear on a largest number of enrolled patients.

Wider implications of the findings: BMI should be carefully taken into account to propose eSET strategy. However, the active use of tobacco should not be considered as a criteria of exclusion in a good prognosis infertile population.
Study funding/competing interest(s): The authors declare no funding or competing interests.
Trial registration number: No need.

O-175 Obesity and impaired uterine receptivity: clinical experience from 9,587 first cycles of ovum donation
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Study question: Does female obesity affect uterine receptivity?
Summary answer: Female obesity impairs reproductive outcome in ovum donation by reducing uterine receptivity.
What is known already: The negative impact of female obesity on uterine receptivity by using the ovum donation model has been a matter of debate in the last decade with scarce publications showing contradictory results. The lack of a correct characterization of the population included and the limited sample sizes analyzed have been the two most important shortcomings in the design of these reports.

Study design, size, duration: Twelve-year (January 1, 2000 to December 31, 2011) retrospective cohort analysis of IVF lab parameters and reproductive outcome measures in 9,587 well-characterized first ovum donation cycles.
Participants/materials, setting, methods: Nine thousand five hundred and eighty seven first cycles of ovum donation coming from normoweight donors were divided according to the BMI (weight /height²) of the recipient to analyze the IVF lab and outcome parameters (implantation, pregnancy, miscarriage and live-birth rates), obtaining four groups: lean with BMI < 20 kg/m² (n = 1,458; 15.2%); normal with BMI 20 to 24.9 kg/m² (n = 5,706; 59.5%), overweight with BMI 25 to 29.9 kg/m² (n = 1,770; 18.5%), and obese with BMI ≥ 30 kg/ m² (n = 653; 6.8%). All these cycles were performed in three settings (Valencia, Madrid, Barcelona) of the same institution (IVI) using the same protocols.

Main results and the role of chance: There were no differences in age, BMI and ovarian stimulation parameters among donors of the four study groups. Overweight or obese recipients were slightly older and presented longer time of infertility. IVF laboratory parameters were similar among BMI groups. However, implantation, pregnancy, clinical pregnancy, twin pregnancy and live birth rates were significantly reduced as BMI increased. In the underweight, normoweight, overweight and obese groups, percentages of blastocysts with optimal morphokinetics were 40.4%, 39.9%, 38.5% and 30.9% (p < 0.001), clinical pregnancy rate was 56.9%, 55.9%, 54.3% and 45.3% (p < 0.001), and live birth rate was 38.6%, 37.9%, 34.9% and 27.7% (p < 0.001), respectively. However, clinical miscarriage rates did not differ among groups. The relative risk reduction of live-birth rates compared with the normoweight group was 1.02 (95%CI 0.90-1.14; p = 0.783), 0.92 (0.82-1.04; p = 0.180) and 0.73 (0.57-0.93; p = 0.006) for the underweight, overweight and obese groups, respectively.

Limitations, reason for caution: Retrospective study. Maternal health information was incomplete in the second and third trimesters of pregnancy. Male partner obesity, smoking habit, distribution of fat, or associated pathology, especially PCOS, was not detailed in the database.

Wider implications of the findings: Female weight excess impairs human reproduction. The reduction of uterine receptivity is one the mechanisms involved. Therefore, weight reduction before pregnancy is advisable in any type of conception including ovum donation.
Study funding/competing interest(s): None
Trial registration number: None

O-176 Time-lapse and array CGH evaluation of human embryos cultured in single versus sequential media: a randomized pilot study
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Study question: Are there differences in the morphokinetics and ploidy of human embryos cultured in single versus sequential media?
Summary answer: The key morphokinetic parameters and percentage of euploid blastocysts are similar between the one-step culture with single continuous media and the two-step culture with sequential media. The one-step culture with the single continuous media is an effective method of culturing human embryos to blastocyst stage.

What is known already: Key morphokinetic markers are highly correlated with implantation potential of embryos which include t5 (time of cleavage to 5 cells), c22 (time between division to 2 and 3 cells) and s2 (time between division to 3 and 4 cells). Recent time-lapse studies comparing single and sequential media show that the key morphokinetic markers remain similar regardless of culture media. However, the chromosomal compositions of the embryos had not been determined in the previous studies.
Study design, size, duration: 561 MII oocytes from 63 patients, ages of 28-39, undergoing preimplantation genetic screening were randomized into two groups after ICSI: A) One-step culture: oocytes (n = 281) were cultured in continuous single culture media (CSC, Irvine Scientific) and B) Two-step culture: oocytes (n = 280) were cultured in sequential media (G1/G2, Vitrolife).
Participants/materials, setting, methods: The key morphokinetic markers were monitored and compared between the two groups. Embryos were cultured to blastocyst stage. 3-5 trophectoderm cells were biopsied on day 5 and analyzed by array CGH. One to two euploid blastocysts with optimal morphokinetics were transferred to individual patients on day 6.

Main results and the role of chance: There were no significant differences in percentage of blastocysts with optimal morphokinetics between the one-step culture (Group A) and the two-step culture (Group B) (52.0% vs. 48.3%, respectively, p > 0.05). There was a non-significant trend towards more embryos developing to euploid blastocysts in Group A compared to Group B (42.4% vs. 35.6%, respectively, p > 0.05). The clinical pregnancy rates were comparable between Group A and Group B (63.2% vs. 56.3%, respectively, p > 0.05). Moreover, the observed implantation rate in Group A was similar to that of Group B (56.7% vs. 52.0%, respectively, p > 0.05).

Limitations, reason for caution: Results are based on observations with embryos from patients undergoing preimplantation genetic screening and may not fully generalize to all patients with different indications.

Wider implications of the findings: For culture from zygote to blastocyst stage, the one-step culture with the continuous single culture media has been shown to be as good as the two-step culture with the sequential media. While minimizing exposure of embryos to the ambient atmosphere and reducing the stress on the embryos, one-step culture with the continuous single media offers additional advantages over the two-step culture with the sequential media.

Study funding/competing interest(s): This study is supported by internal funding. All authors report no competing interests.
Trial registration number: Not applicable.

O-177 Aberrant DNA methylation of GRB10 gene in human spontaneous abortions after assisted reproduction techniques and natural conception
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Study question: Would GRB10 be a candidate gene related to human spontaneous abortion (SA)?
Summary answer: Imprinting errors of GRB10 gene may contribute to human SA, and the aberrant GRB10 methylation patterns may not be related to assisted reproductive technologies (ART) procedures.

SELECTED ORAL COMMUNICATION SESSION
Session 46: Epigenetics in reproductive health
Tuesday 9 July 2013 17:00 - 18:00